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Synthesis of alpha-Galactosylceramide Analogs for Th1 Biased iNKT Cell Activation and Novel Reactions with Ketiminium Salts

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NKT Cell Activation

and Novel Reactions with Ketiminium Salts

Nicole Sassu, Ph.D.

University of Connecticut, 2018

Natural killer T (NKT) cells are a subset of T cells that recognizes and is activated by glycolipid antigens. Glycolipids, specifically α -galactosylceramides, are a primary focus due to their ability to modulate immune responses based on interactions with NKT cells. KRN7000, the first synthetic glycolipid shown to potently activate NKT cells, has been the foundation of structure-activity relationship (SAR) studies, providing insight to how glycolipids interact with components of the immune system to elicit specific responses. A glycolipid can produce a Th1 and/or Th2 response from NKT cells. A primary goal of many researchers is to produce a potent glycolipid, but also one that selectively induces a Th1 response.

Various modifications have been made to the structure of KRN7000 to monitor changes in activity. 7DW8-5 is a potent, Th1 biasing glycolipid that emerged from such efforts. Another modification to KRN7000 was replacing galactose with several disaccharide counterparts. Certain disaccharides have been shown to increase Th1 responses in whole cell assays. Therefore, this thesis describes novel analogs of 7DW8-5 that have been developed in an attempt to produce a potent, Th1 biased biological response.

Chiral amines are abundant in pharmaceutically interesting compounds including drugs currently on the market. One method of generating chiral amines is through nucleophilic addition into chiral *N*-sulfinyl imines and other substituted imines. One major flaw in this method is that the synthesis of *N*-substituted imines is not trivial. Some methods require highly reactive species or form insoluble byproducts that are not viable for large-scale process chemistry set ups. Transimination has been shown to form *N*-alkyl substituted ketimines from a ketiminium salt and alkyl amine. This thesis presents the first use of transimination to form chiral *N*-sulfinyl ketimines under optimal conditions. Ketiminium salts were also used to generate a library of *N*-phosphinyl, -tosyl, and -carbamoyl ketimines under mildly basic conditions with good to excellent yields.

**Synthesis of α -Galactosylceramide Analogs for Th1 Biased
iNKT Cell Activation
and Novel Reactions with Ketiminium Salts**

Nicole Sassu

B. Sc., Providence College, 2013

A Dissertation

Submitted in Partial Fulfillment of the

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2018

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Nicole Sassu

2018

APPROVAL PAGE

Doctor of Philosophy Dissertation

Synthesis of α -Galactosylceramide Analogs for Th1 Biased *NKT* Cell Activation
and Novel Reactions with Ketiminium Salts

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2018

To my loving, supportive family and most importantly,

Gary and Veronica Sassu

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chemistry at hand, running, and life in general. He also helped me shred a few seconds off my average mile time on long runs, and for that, I thank you!

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LIST OF ABBREVIATIONS

Ac	Acetate
AcOH	Acetic acid
APC	Antigen presenting cell
aq	aqueous
Bn	Benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	Benzoyl
CBz	carboxylbenzyl
CD1d	Cluster of differentiation
CDCl ₃	Deuterated chloroform
CHCl ₃	Chloroform
d	day

DCC	<i>N,N'</i> -Dicyclohexyl carbodiimide
DCM/CH ₂ Cl ₂	Dichloromethane
DIBAL-H	Diisobutyl aluminum hydride
DMAP	4-Dimethylaminopyridine
DMDO	dimethyldioxirane
DMSO	dimethyl sulfoxide
DMF	Dimethylformamide
EDC	1-[3-(dimethylamino)propyl]3-ethylcarbodiimide
equiv	equivalents
ESI	Electrospray ionization
Et ₃ N	Triethyl amine
Et ₂ O	Diethyl ether
EtOAc	Ethyl acetate
α-GalCer	alpha galactosylceramide
GSL	glycosphingolipids
h	hours
HCl	Hydrochloric acid
HRMS	high resolution mass spectrometry
Hz	Hertz
IFN-γ	interferon-gamma
IL-4	interlukin-4
IR	infrared
MeOH	Methanol

MgSO ₄	Magnesium sulfate
NaH	Sodium hydride
NaHCO ₃	Sodium bicarbonate
NaOMe	Sodium methoxide
NH ₄ Cl	Ammonium chloride
NIS	<i>N</i> -iodosuccinimide
OTf	Triflate
Pet. Ether	Petroleum ether
Piv	pivaloyl
PNP	p-nitrophenyl
Pyr	pyridine
rt	Room temperature
SAR	structure-activity relationship
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBS/TBDMS	<i>tert</i> -butyldimethylsilane
TBDPS	<i>tert</i> -butyldiphenylsilane
TCR	T-cell receptor
TFA	Trifluoroacetic acid
Th	T helper
THF	Tetrahydrofuran
TOF	time of flight
Trt	Trityl
Ts	<i>p</i> -toluenesulfonyl

CHAPTER 1

Synthesis of α -Galactosylceramide Analogs for Th1 Biased NKT Cell Activation

1.1 INTRODUCTION

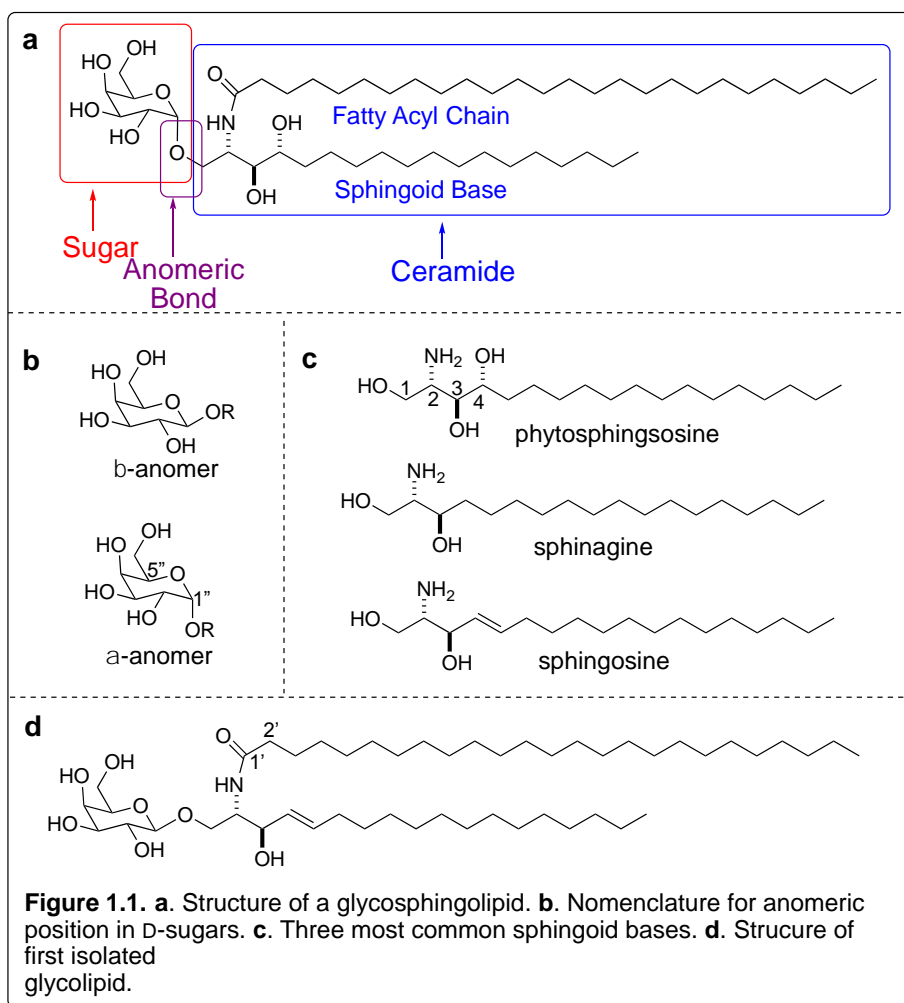
1.1.1 Natural Killer T Cells

Natural killer T (NKT) cells are members of both the innate and adaptive immune system. The T cell receptors (TCRs) of NKT cells recognize lipid antigens presented by CD1d proteins on the surface of antigen presenting cells (APCs). It has been shown that genetically engineered mice deficient in CD1d fail to develop NKT cells. As a result, the immune system is unable to protect against common infections, and the mice do not survive. This result indicates the absolute necessity of these cells to the immune system.¹ NKT cells can further be classified into two distinct groups: Type I and Type II. Type I NKT cells express an invariant T cell receptor (iNKT cells) whereas Type II express a diverse set of TCRs. Although the most abundant NKT cells in humans are Type II, Type I NKT cells have been studied more extensively with lipid antigen activators.²

1.1.2 Glycosphingolipids

Glycosphingolipids (GSLs) are a class of amphiphilic natural products. Due to both their polar and nonpolar nature, these compounds are found in the cell membranes of both prokaryotes and eukaryotes.³ The name glycosphingolipids denotes the general structure of this class of compounds. They contain a polar sugar head with two lipid tails characterized as a fatty acyl chain and sphingoid base. The two lipid tails together are

referred to as a ceramide (Fig. 1.1a). Glycosphingolipids can be further characterized by the arrangement of the glycosidic linkage, the degree of saturation on the sphingoid base, as well as which sugar is present on the polar head. The anomeric substituent can be either in the α or β disposition. For D-sugars, which are most commonly found in nature, when the anomeric substituent is axial, it is considered alpha (α), because it is anti to the C5'' substituent. When the C1'' and C5'' substituents are syn in D-sugars, they are considered beta (β) (Fig. 1.1b). The same nomenclature applies when there are more than one sugar present on the glycolipid. Di- and tri-saccharide glycolipids have also been isolated. Although the sphingoid base can vary, there are three very common types:

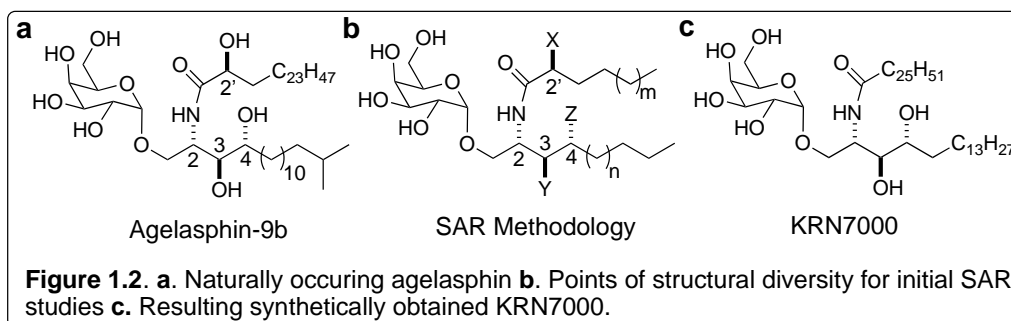


phytosphingosine, sphinganine, and sphingosine. Phytosphingosine is an amino triol,

whereas sphinganine is an amino diol with the C4 hydroxyl in phytosphingosine replaces with a proton. The C4 hydroxyl is eliminated in sphingosine with an alkene between the C4 and C5 (Fig. 1.1c). Following the nomenclature for glycosphingolipids, the compound in Figure 1.1a can also be called an α -Galactosylceramide (α -GalCer), due to the anomeric carbon position and galactose sugar head. The first natural glycosphingolipid isolated and characterized was a β -GalCer with a sphingosine base (Fig. 1.1d).⁴ Like the natural product in Figure 1.1d, most naturally occurring glycosphingolipids are β -linked, with the predominant sugars being galactose or glucose.⁵ However, α -GalCers have also been isolated and are of great pharmaceutical interest.

1.1.3 KRN7000

In 1993, Kirin Brewery, a subsidiary of Kirin Holdings Company in Japan, reported the activity of several isolated glycosphingolipids, termed agelasphins, from the marine sponge *Agelus maritimus*.⁶ Agelasphin-9b was a potentially interesting natural product, because it was shown to have anti-tumor activity in B-16 melanoma mice (Fig. 1.2a). Using agelasphin-9b as a lead compound, structure-activity relationship (SAR) studies were performed.⁷



Because agelasphin-9b's activity was measured on the isolated natural product, Morita et al. also sought to synthesize the glycolipid to ensure that the compound's activity was not due to unknown natural product impurities. Luckily, both the isolated and synthesized natural product had the same reactivity, confirming the glycolipid's biological effect. In generating agelasphin-9b, however, the synthetic chemists noted how difficult it was to establish a terminal branched methyl in the sphingoid base. Therefore, while performing SAR studies, they generated a library of compounds similar to agelasphin-9b, differing in C-3, C-4, and the length of the sphingoid base (n), while monitoring the effect of a linear sphingoid base versus branched. They also sought to observe the effect of substitution on C-2' as well as the length of the acyl chain (m). Including agelasphin-9b, they reported the activity of twenty glycolipid analogs where X, Y, and Z in Figure 1.2b was either a hydroxyl group or a proton, the acyl chain length ranged from thirteen to twenty-five carbons, and the sphingoid base ranged from eleven to eighteen carbons.

When monitoring tumor growth inhibition in B16 melanoma bearing mice, no difference in effect was observed between branched and linear sphingoid bases. When comparing the length of the linear sphingoid base (C-11, C-15, C-18, C-19, and C-20), it was found that the eighteen carbon sphingoid base had the most inhibitory activity. Another murine assay was performed to measure lymphocyte proliferation (LP). The researchers found that when there were no alcohols on the sphingoid base, no LP is observed. It was also noted that a similar LP response was observed in the 3,4-dihydroxy and 3-hydroxy analogs. These results led the researchers to conclude that, although the 3-OH was necessary for biological activity in mice, the 4-OH may not be. In the same murine assays, it was also found that a longer acyl chain (C-25) had the best results and the 2'-OH did not play an

important role, if any, in biological activity. The glycolipids with promising biological activity were then carried forward into human umbilical cord blood (hUCB) assays. Interestingly, compounds with 3,4-dihydroxy sphingoid bases performed better than 3-hydroxy. This result indicated that the 4-OH may play a more important role for activity in human cells than it does in mice biological activity. The results of the SAR study are summarized in Table 1.1.

Putting all the results together led to a simplified and synthetically accessible glycolipid, KRN7000 (Fig. 1.2c). KRN7000 was chosen as the desirable candidate to carry forward into clinical trials.⁸ Since its development, KRN7000 has remained the gold standard for glycolipid activity of which all other glycolipid analogs are compared to.

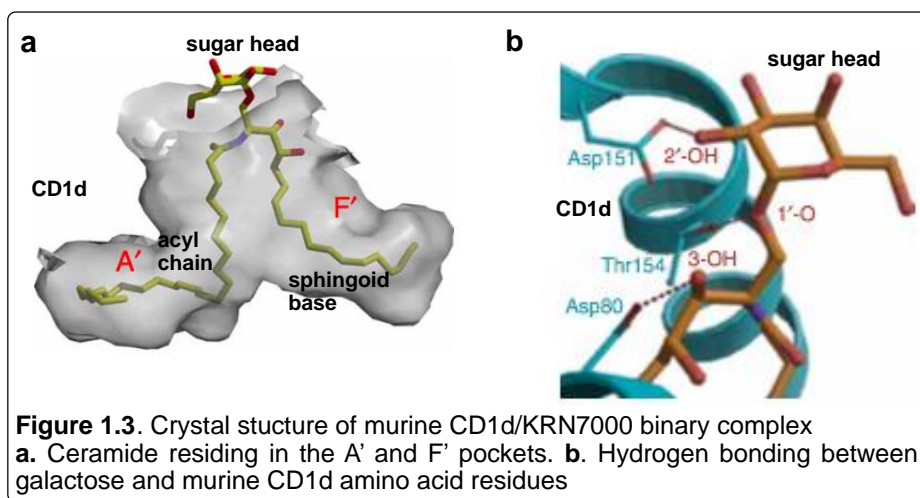
Table 1.1. Summary of SAR study performed on agelasphin-9b

Structural Feature	Activity
2'-OH (X)	No significant effect
3-OH (Y)	Required for activity
4-OH (Z)	-Not required for activity in mice -Required for improved activity in humans
Branched sphingoid base	No significant effect
Short acyl (m)	Less active
Long acyl (m)	More active (25 carbon chain best)
Short sphingoid base (n)	Less active
Long sphingoid base (n)	More active (18 carbon chain best)

1.1.4 Glycosphingolipid Mechanism of Action

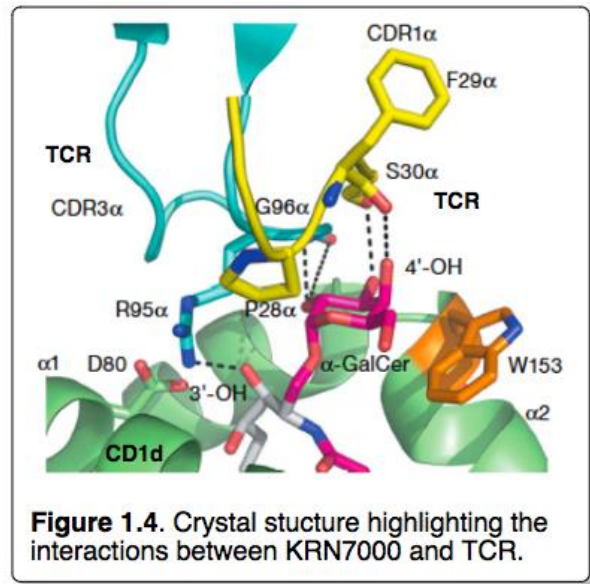
When agelasphin-9b and other glycolipid analogs were first found to be tumor growth inhibitors, the mechanism of action was not fully understood. In 1997, it was discovered that glycolipids, such as KRN7000, are CD1d-restricted activators of NKT cells via TCRs.⁹ When glycosphingolipids were exposed to antigen presenting cells (APCs), more specifically CD1d proteins on the cells, they were found to follow an immunological

pathway. A glycosphingolipid is considered an antigen by the immune system, and this is recognized by APCs. APCs contain CD1d proteins on the surface of the cell which bind lipid antigens. The long hydrophobic tails of the ceramide fit into an active site of CD1d forming a binary complex. Mice CD1d proteins contain two hydrophobic pockets, termed A' and F', that are lined with hydrophobic amino acid residues. The fatty acyl chain docks into the A' pocket, whereas the sphingoid base resides in F'. Due to difficulties isolating the human CD1d (hCD1d)/glycolipid binary complex, only the murine binary complex has been reported (Fig. 1.3a).¹⁰



Alcohols on the sugar and sphingoid base of KRN7000 also interact with CD1d via hydrogen bonding which further stabilizes the binary complex (Fig. 1.3b).¹¹ The 2''-OH of galactose participates in hydrogen bonding with Asp151 on CD1d, and the 1-O and 3-OH of phytosphingosine hydrogen bond with polar amino acids Thr154 and Asp80, respectively. As mentioned previously, the 4-OH of KRN7000 is required for increased activity in human cells, but no significant interaction has been observed in the murine (binary) or human (ternary) crystal structures.

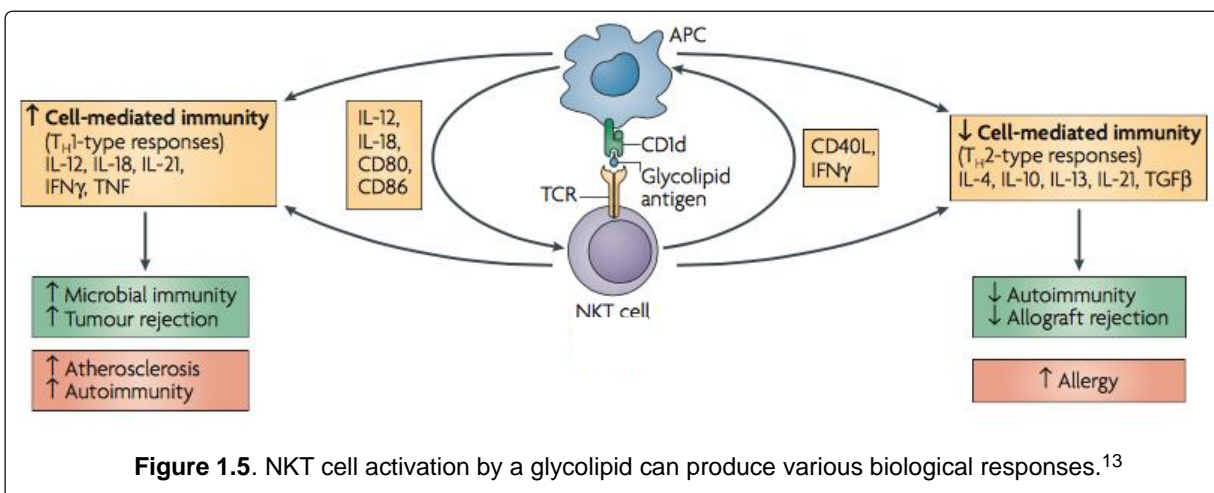
Invariant TCRs (*inv*TCRs) on the surface of NKT cells recognize binary complexes (APC/GSL) presented by the APC to form the ternary complex (APC/GSL/NKT). Because KRN7000 protrudes out of the APC minimally, few interactions between galactose and the TCR have been observed in both mice and human NKT cells. A crystal structure of the ternary complex solved by



Rossjohn and co workers highlights the interactions between glycosyl alcohols on KRN7000 and a human TCR on an NKT cell (Fig. 1.4).¹² The 3"-OH and 4"-OH on galactose interact with the CDR3 α and CDR1 α loop on the TCR, respectively. The amino acid sequences of these loops are conserved between mice and human TCRs. Key interactions occur between the 3"-OH and Arg95 α on CDR3 α and between the 4"-OH and Ser30 α on the CDR1 α loop. These hydrogen bonding interactions contribute to the overall stability of the ternary complex. This indicates the importance of the 4"-OH and 3"-OH on galactose for TCR interaction.

Once the ternary complex is formed, NKT cells are stimulated. Glycolipids can promote both a Th1 and Th2 response, which results in the development and release of various cytokines (Fig. 1.5).¹³ The Th1 response is characterized by the production of interferon-gamma (IFN γ), interleukin 2 (IL-2), and tumor necrosis factor (TNF), among others. These cytokines cause a pro-inflammatory response, which in turn fights infections and tumor

growth. Conversely, the Th2 response is considered anti-inflammatory, and the Th2 cytokines, IL-4, IL-10, and IL-13, prevent autoimmune diseases from developing.



1.1.5 Th1 and Th2 Biasing Effects

Because glycolipids were first shown to have tumor growth inhibiting effects, efforts have continued to modify the structure of glycolipids, such as KRN7000, to produce the optimal anti-tumor biological response. Due to the antagonistic effects of the Th1 and Th2 responses, the target glycolipid therapy would invoke an ideal balance of Th1 versus Th2. Although promoting a Th1 response can result in the treatment of infections and tumors, too much stimulation of Th1 cytokines results in autoimmune disease development. Similarly, although a Th2 response can counteract autoimmune disorders, an excess of Th2 cytokines can lead to allergic inflammatory diseases.¹⁴ Despite KRN7000's ability to induce an immune response, it has been largely a failure in clinical trials for the treatment of metastatic cancer.¹⁵ This result is thought to be due to the stimulation of both a Th1 and Th2 response, which negates the overall effectiveness of the treatment. Therefore, for a glycolipid cancer therapy to be successful, it is critical to elicit the perfect balance of

both immune responses to achieve the desired result. Unfortunately, the optimal Th1/Th2 ratio is not fully understood, and as a result, researchers continue to seek a glycolipid that can produce enough of a biased Th1 response to have a significant and positive biological effect, while also inducing an adequate Th2 response so as to not cause harm.

1.1.6 Structural Modifications to KRN7000

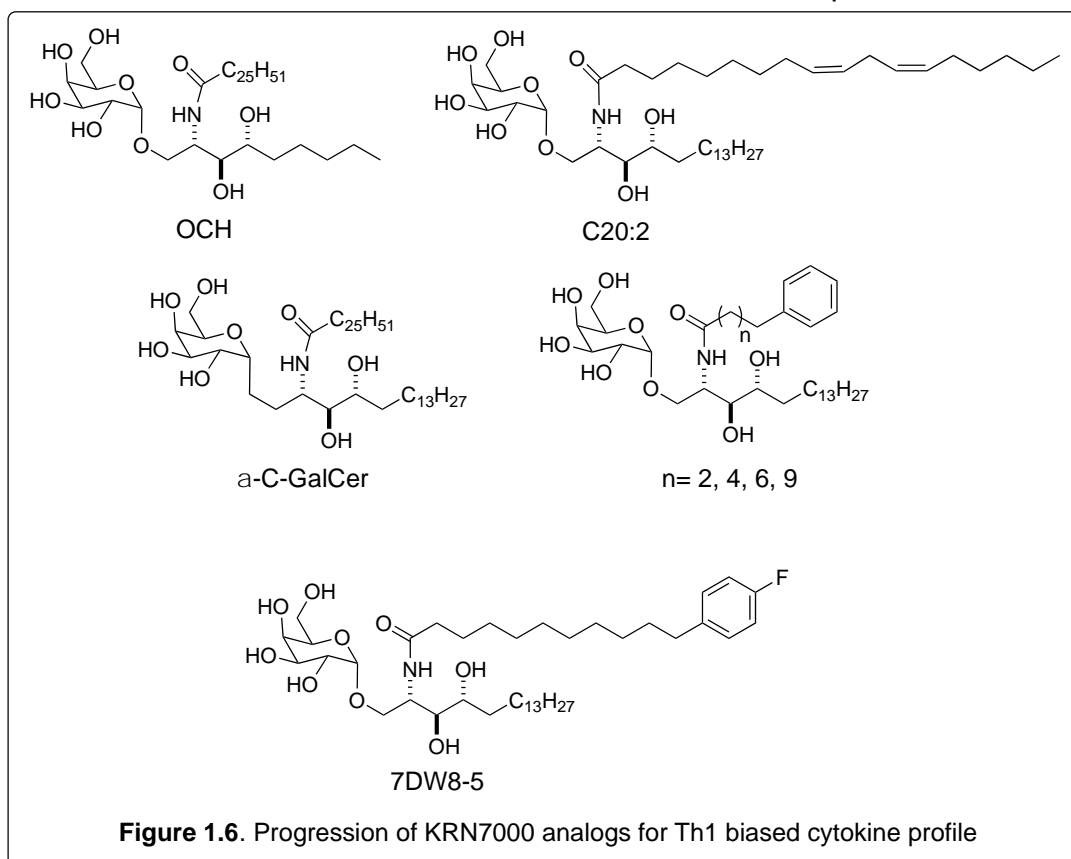
Because KRN7000 showed greater potency than most synthetically obtained GSLs but had poor Th1 selectivity, many groups have sought to modify KRN7000 in order to maintain potency yet produce a polarizing Th1 effect.

1.1.6.1 Acyl Chain Modifications

As mentioned previously, the first source of glycolipid recognition by CD1d is at the lipid tails of the ceramide in the hydrophobic A' and F' pockets. Therefore, Yamamura and co workers explored the effect of the hydrocarbon chain length on the sphingoid base. Despite the objective of biasing a Th1 response, one analog with a truncated sphingoid base resulted in a Th2 cytokine profile.¹⁶ This glycolipid, termed OCH, was not as potent as KRN7000, but was interesting nonetheless (Fig. 1.6). Due to its Th2 biasing nature, it was shown to activate NKT cells in mice and treat autoimmune encephalomyelitis, the murine equivalent of multiple sclerosis. Soon after, another glycolipid was reported to be less potent than KRN7000, but more Th2 biasing (C20:2).¹⁷ C20:2 was similar to KRN7000 in the sphingoid base, but contained a skipped diene in the shortened acyl chain.

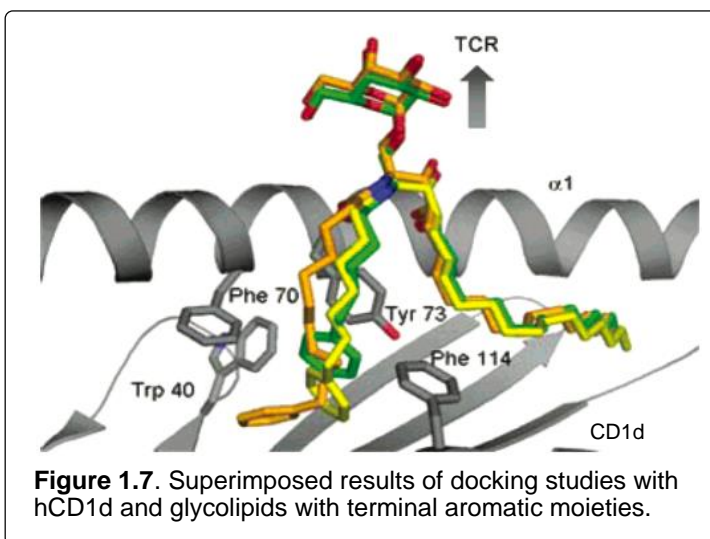
The first glycolipid to show a significant Th1 cytokine profile was α -C-GalCer, which differs from KRN7000 solely at the anomeric position with a methylene replacing the anomeric

ether.¹⁸ Although it was shown to have a stronger Th1 biased response in B16 melanoma mice assays, it later failed in human lymphocyte studies.¹⁹ Similar to C20:2, more SAR studies were performed on the acyl chain of KRN7000. It wasn't until aromatic moieties were incorporated into the acyl chain that a Th1 cytokine profile was observed again. In 2006, Wong and co workers reported a library of glycolipids with acyl chains of varying length and aromatic rings.²⁰ Although they examined the effect of heteroaromatics such as pyridine, thiophene, and furan, most interesting were the glycolipids with shortened hydrocarbon tails with a terminal phenyl group (see Fig. 1.6). These glycolipids were shown to bias a Th1 response by about 2:1 based on the levels of IFN- γ and IL-4 measured. Docking studies with hCD1d revealed similar interactions in the F' pocket observed with phytosphingosine of KRN7000. Significantly different from KRN7000 were the interactions with aromatic amino acid residues in the A' pocket observed in the



modeling program, Autodock 3.0, employed for docking studies (Fig. 1.7).²¹ These interactions included pi stacking between the phenyl rings on the glycolipids with a chain length of five and seven carbons and the phenol of Tyr73. Similarly, pi interactions between the GSL with ten carbons and Trp40 were also noted. Shorter aromatic acyl chains had few significant interactions in the A' pocket.

In biological assays, these aromatic substituted compounds had greater anti-cancer activity than KRN7000 in breast and lung cancer models.²² This biological result could be due to the aromatic analogs demonstrating up to an 80-fold greater binding affinity to CD1d than KRN7000, implying the more stable the binary complex, the more Th1 biasing.²³ Another aromatic glycolipid that contained eight carbons in the acyl chain with a terminal *p*-fluorophenyl group was examined. It was shown to have the highest number of van



der Waals contacts in the A' pocket. Based on these results, it was determined that aromatic substituents on the acyl chain promote a beneficial IFN- γ /IL-4 ratio and fine tune the Th1/Th2 response.

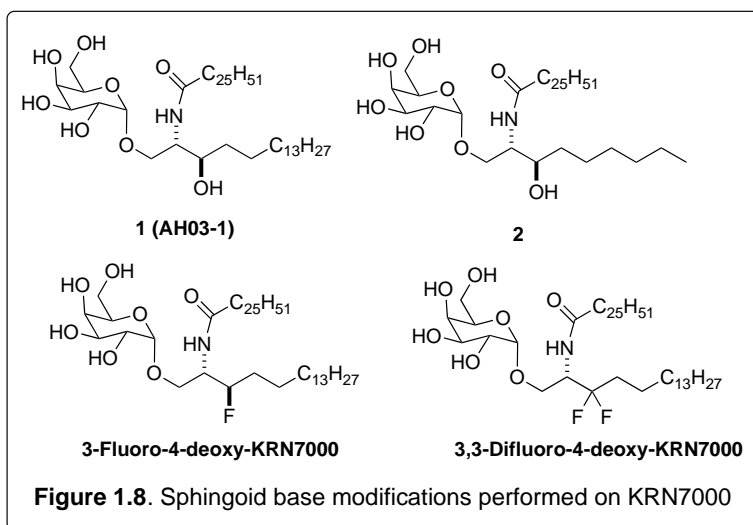
One additional important analog with an acyl chain modification has been examined by Wong and co workers. In 2010, 7DW8-5, with ten carbons and a terminal *p*-fluorophenyl group on the acyl chain, was reported to have potential as a vaccine adjuvant (see Fig. 1.6).²⁴ An adjuvant is an immunological agent that promotes the immune response to a

vaccine. As a result, the adjuvant increases the efficacy of said vaccine by producing a greater number of antibodies for longer-lasting immunity. Because α -GalCers are proven to boost immunological activity, they have been examined as potential vaccine adjuvants.²⁵ 7DW8-5 produces a much greater Th1 response than KRN7000 with significantly more IFN- γ and IL-2 production. 7DW8-5 also has a drastically lower half maximal effective concentration (EC_{50}) value against human \mathcal{N} KT cells than KRN7000: 0.38 nM and 54 nM respectively. EC_{50} is an operational value measured for potential drugs. It refers to the concentration of a drug required to induce a response that is halfway between the baseline and maximal measurement of a biological response.²⁶ EC_{50} is typically used to measure how potent a drug is. A low (sub-nanomolar) EC_{50} indicates a more effective drug, because it takes a smaller dose to induce the same result. Furthermore, 7DW8-5 has a much lower dissociation constant (K_d) to *inv*TCRs than KRN7000. Once again, the lower the K_d value, the greater the binding affinity. Overall, 7DW8-5 exhibited a greater Th1 response at much lower concentrations than KRN7000, suggesting it is a promising therapeutic agent with multiple functions.

1.1.6.2 Sphingoid Base Modifications

As mentioned in the SAR study of agelaphin-9b, Morita and co workers investigated the effect of the 4-OH on glycolipids. Surprisingly, the twenty analogs examined in the SAR study did not include a sample of KRN7000 with a sphinganine sphingoid base. Analogs missing the 4-OH, had varied sphingoid base and acyl chain lengths that did not match KRN7000. Therefore, the sphinganine analog of KRN7000 had remained unexamined for quite some time. In 2004, the Howell group reported various methods of accessing

sphinganine-type sphingoid bases (aminodiols).²⁷ At the time, these syntheses were much simpler than generating phytosphingosine, which has since become commercially available for a reasonable cost. As a result of that work, the Howell group reported the first synthesis of both KRN7000 and OCH analogs containing a sphinganine base in 2005 (Fig. 1.8).²⁸ Biological assays using immortalized NKT cells revealed that **1 (AH03-1)** and **2** had comparable activity to their phytosphingosine counterparts. **AH03-1** elicited a strong Th1 response in mice but did not perform as well in human cell lines. These results confirm what Morita and co workers observed that the 4-OH may not be crucial to a glycolipid's activity in mice, but plays a larger role in human

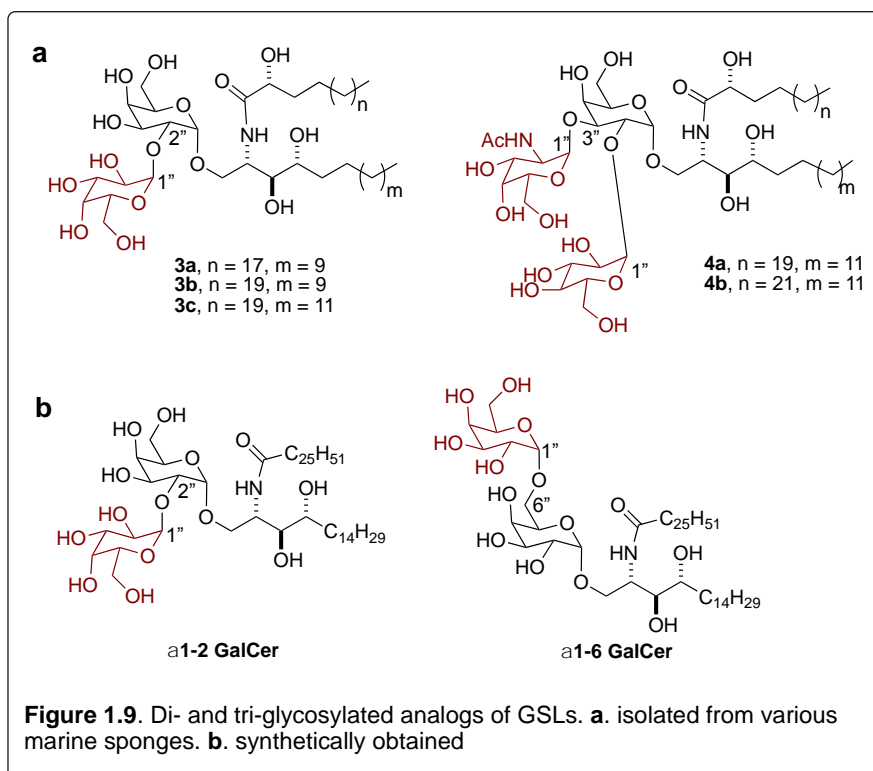


CD1d docking. There continues to be conflicting reports about the importance of 4-OH in the sphingoid base. Pipelier and co workers generated KRN7000 analogs with 3-fluoro and 3,3-difluoro substitutions. Both analogs were 4-deoxy, and they argued their analogs work as well as KRN7000 in human NKT cell models.²⁹ Analogs without any functional group at C3 or C4 were not investigated due to reports of their inactivity.³⁰ Glycolipids containing an unsaturated sphingosine base have also been investigated but these compounds are typically β -GalCers and β -GlcCers and interact with the immune system in a different manner.³¹

1.1.6.3 Carbohydrate Modifications

As with the other components of a GSL, the sugar head has also been modified for SAR studies. Disaccharide analogs of α -GalCers are of interest partially due to the isolation and characterization of naturally occurring di-glycosylated GSLs (Fig. 1.9a). **3a-c** and **4a,b** were isolated from an unknown Japanese marine sponge and *Stylissa frabeliformis* respectively.³² Compounds **3a-c** are di-glycosylated GSLs with an α glycosidic linkage between two galactoses at C1'' and C2''. Therefore, they are considered α (1-2) glycolipids. Following the same nomenclature, **4a** and **4b** are α (1-2, 1-3) GSLs. Not surprisingly, **4a** and **4b** had diminished immunological activity, which could be rationalized by a loss in the H-bonding of 3''-OH with the TCR shown in Figure 1.4. GSLs **3a-c** were examined for their effects on mixed lymphocyte reaction (MLR) and murine spleen cell proliferation. MLR is a pharmaceutical safety assay where different lymphocyte populations are mixed together with the compound of interest and the cellular reaction is recorded. The purpose of the assay is to measure how T cells react to certain species.³³ Although this assay does not indicate exactly how the glycolipids are activating NKT cells, it serves as a starting point to see if a compound is active at all and whether or not it should be carried forward for more extensive studies. Compounds **3b** and **3c** had comparable activity in the MLR assay, whereas **3a** was significantly less potent. This result was somewhat perplexing considering **3a** has just two fewer carbons in the acyl chain than **3b**. Spleen cell proliferation studies also showed a much weaker response to **3a**. These results indicate that the length of the hydrocarbon acyl chain plays a role in the activity of the glycolipid, and the longer the chain, the better the activity; as shown with **3b**, **3c**, and KRN7000.

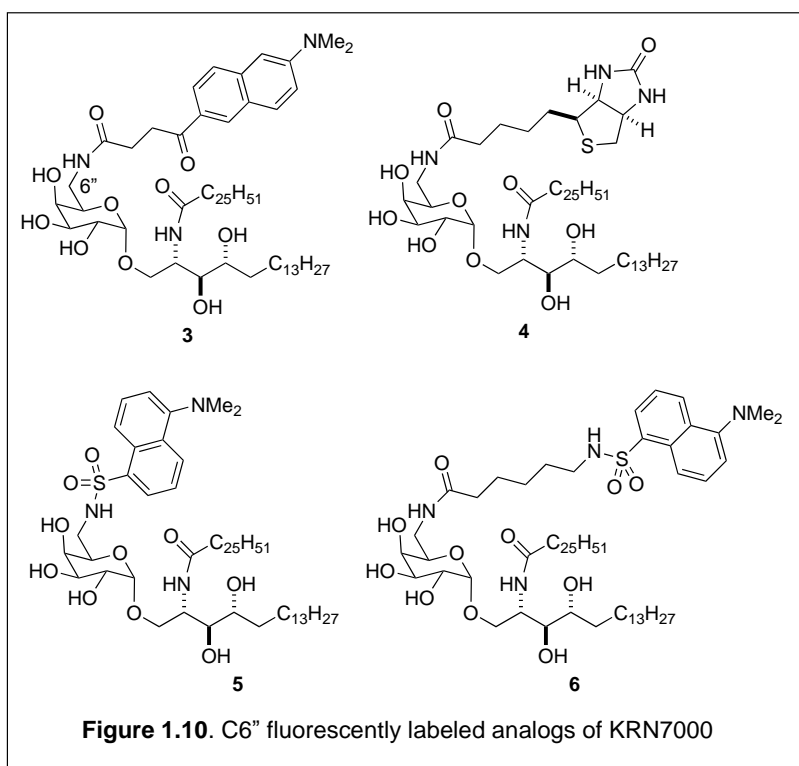
In 1997, the Kirin Brewing Company once again reported on the activity of KRN7000-type glycolipids.⁹ This time, they explored the activity of disaccharide analogs of KRN7000. In 2001, the glycolipids were sent to Kronenberg and co workers, who reported the cellular processing of the disaccharide analogs of KRN7000 (Fig. 1.9b).³⁴ Following the naturally-occurring agelasphin analogs, they reported the $\alpha(1-2)$ analog of KRN7000. Because the $\alpha(1-3)$ was previously found to be inactive, they investigated an $\alpha(1-6)$ analog instead. One purpose of the study was to observe what kind of antigen processing, if any, the disaccharides underwent in the presence of cellular enzymes such as α -galactosidase, a sugar-cleaving enzyme. In an APC-free T cell stimulation assay, KRN7000 and $\alpha(1-6)$ GalCer were able to stimulate IL-2 production by NKT cells whereas $\alpha(1-2)$ GalCer was not. This test uses mouse CD1d coated plates to examine whether the lipid antigens require internalization and cellular processing to activate NKT cells or if they can just bind



to CD1d and cause an immunological response. Because $\alpha(1-2)$ GalCer resulted in no IL-2 release, it must require some degree of processing. Interestingly, they observed NKT cell stimulation in assays with CD1d on APCs and $\alpha(1-2)$ GalCer, indicating that the presentation of $\alpha(1-2)$ GalCer to the TCR may occur after CD1d is internalized directed to antigen processing compartments in the APC. To test this hypothesis, a fluorescent assay was employed where they were able to observe CD1d immunolocalized in APCs using Bodipy-labelled pepstatin. Conversely, KRN7000 and $\alpha(1-6)$ GalCer were not internalized upon formation of the binary complex. Similarly, when Bafilomycin A1 (Baf), an inhibitor that prevents cellular uptake of macromolecules, was introduced, both KRN7000 and $\alpha(1-6)$ GalCer promoted IL-2 production, whereas $\alpha(1-2)$ GalCer had no reaction. To confirm $\alpha(1-2)$ GalCer internalization, an analogous assay was performed where APC and $\alpha(1-2)$ GalCer were incubated together; then, Baf was introduced. IL-2 production was observed, meaning $\alpha(1-2)$ GalCer was internalized before Baf could inhibit it, and the GSL was able to activate NKT cells. Finally, an *in vitro* assay was performed to mimic *in vivo* conditions. α -Galactosidase was introduced to the system to examine what cellular processing was required for $\alpha(1-2)$ GalCer activity. They observed a dose-dependent increase of IL-2 and IFN- γ production, mimicking antigen processing in APCs. What was most fascinating however, was that upon $\alpha(1-2)$ GalCer trafficking and processing, the IL-2 and IFN- γ production was greater than that of KRN7000. The results of this extensive study suggest that certain GSLs can be internalized and undergo cellular processing by co-opting metabolic pathways that typically serve another function in the cell. From an SAR standpoint, it was notable that $\alpha(1-2)$ GalCer was more potent and more Th1 biasing than KRN7000 after such processing occurred.

Glycolipid analogs with C6'' modifications have also been investigated. This type of GSL was first used for labelling studies where the fluorescent handle was anchored onto C6''. In 2002, Savage and co workers reported the synthesis of KRN7000 analogs with C6'' amides and sulfonamides linked to fluorescent probes (Fig. 1.10).³⁵ The purpose of the experiment was to follow the GSLs' pathway to activating NKT cells, but what was ultimately interesting from an SAR standpoint is that these C6'' modifications did not disrupt the GSL-induced production of IL-2.

Following this trend, the Savage group then reported the activity of C6'' amides **7a** and **7b** (Fig. 1.11).^{36,37} GSLs **7a** and **7b** are C6'' *N*-acetylated analogs of KRN7000, but **7b**



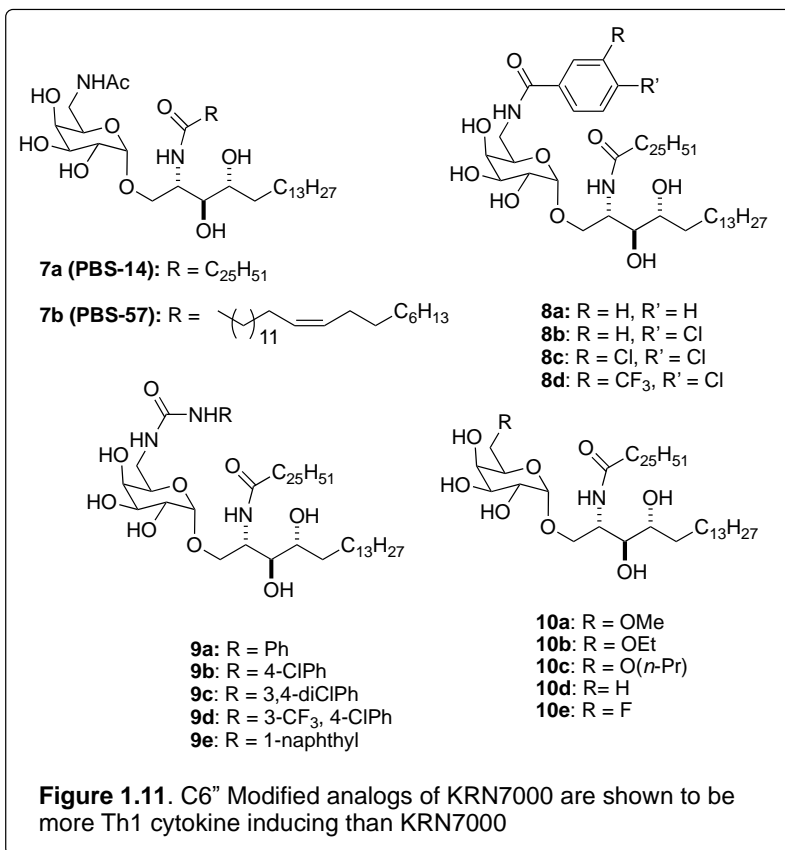
also contains an olefin in the acyl chain. These GSLs were shown to be more potent and Th1 polarizing than KRN7000 during *in vitro* and *in vivo* studies. Thus, for the last decade, synthesis groups have been derivatizing the C6'' alcohol of KRN7000 with various functional groups.

Trappeniers and et al. reported a handful of C6'' amide and carbamate analogs **8a-d** and **9a-e**.³⁸ While **8a** had no agonistic effect, **8b-d** caused decreased production of IL-4 (a Th2 cytokine) while still stimulating a reasonable amount of IFN- γ . This trend was thought

to be due to favorable electron withdrawing effects on the phenyl ring. The CF₃ substituent on **8d** was thought to be why the GSL had such a positive cytokine profile with IFN- γ production similar to that of KRN7000. The C6"-carbamate class of GSLs were found to be Th1 skewing with **9e** resulting in the highest concentration of IFN- γ produced. It outperformed KRN7000 in assays with both human peripheral blood mononuclear cells (PBMCs) and human NKT cells.³⁹ This naphthyl-carbamate has been studied more extensively and is now generally referred to as NU- α -GalCer.

In 2013, the Mori group investigated the effects of ethers at C6" as well as a C6" proton and fluorine.⁴⁰ Their glycolipids (**10a-e**) stimulated mice NKT cells *in vivo* to produce more IFN- γ than KRN7000 while resulting in the same concentrations of IL-4. Interestingly, **10a** had a better cytokine profile than **10b-c** despite there only being a one

and two carbon difference among the three compounds. Because **10d-e** resulted in more Th1 cytokine production than the ethers, the researchers hypothesized that a smaller, hydrophobic group at C6" induces a greater Th1 bias. This conclusion seems to contradict the promising activity of NU- α -GalCer, which, based on their theory, should not be a



1.1.6.4 Combining KRN7000 Modifications

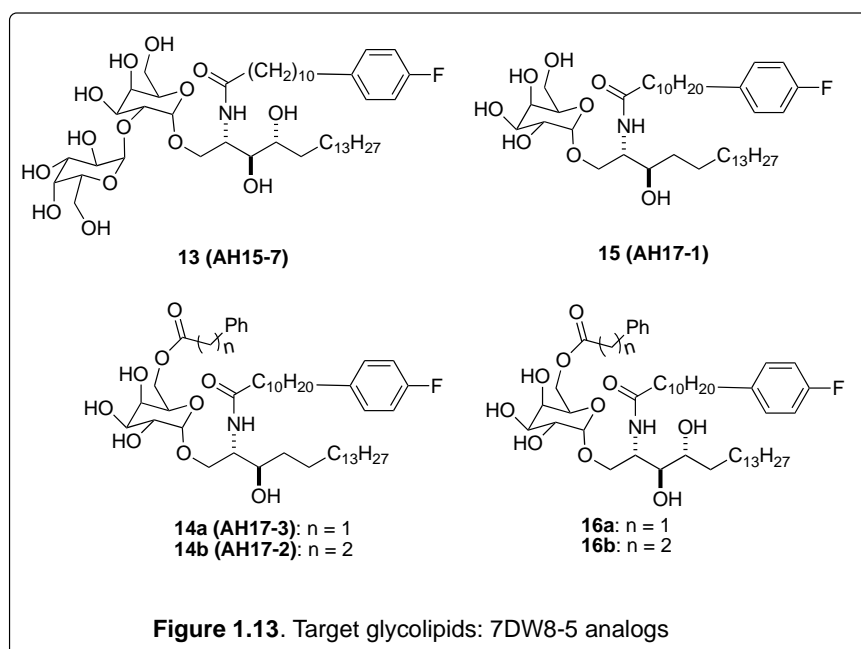
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acids on mCD1d. These interactions are thought to strengthen **AH10-7** and mCD1d binding, thus stabilizing galactose for recognition by the NKT cell via the TCR. The disaccharide series, **AH15-5** and **AH15-6** are still undergoing preliminary biological studies by the Porcelli group at The Albert Einstein School of Medicine.

1.1.7 Target Glycolipids: SAR of 7DW8-5

As mentioned previously, 7DW8-5 produced a better cytokine profile than KRN7000. Although 7DW8-5 has undergone some SAR studies, the modifications were made primarily to the terminal fluorophenyl group.⁴² Wong and co workers explored the addition of substituted biphenyl systems on the acyl chain but found that in most cases, single phenyl rings such as 7DW8-5 performed best. They also explored the effects of a truncated sphingoid base (C8) with a terminal phenyl ring. In these analogs, they found CD1d docking to be greatly diminished. Therefore, to better improve the activity of 7DW8-5, six target analogs were designed that incorporate various structural modifications shown to improve the activity of KRN7000 (Fig. 1.13). This strategy was chosen based on two arguments. A deductive argument: if these modifications make KRN7000 more potent and Th1 biasing, and 7DW8-5 is more potent and biasing than KRN7000, then the same modifications to 7DW8-5 will produce an even more potent and Th1 biasing response than all the previous analogs. A crystal structure-based argument: by incorporating the same C6" esters into 7DW8-5, perhaps the same amino acid interactions would occur that promote the Th1 skewed response seen in **AH10-7**.

The analogs chosen to investigate are a combination of modifications performed by the Howell group and others. Based on the work of Prigozy et al., $\alpha(1-2)$ 7DW8-5 (**13**) was chosen for examination primarily for the promising activity displayed by $\alpha(1-2)$ GalCer upon cellular trafficking and processing. Inspired by the Th1 biasing effect observed in the Howell group's **AH03-1** and **AH10-7**, glycolipids containing a sphinganine base with and without C6" esters were chosen for investigation **14a** (**AH17-3**), **14b** (**AH17-2**), and **15** (**AH17-1**). C6" phenyl esters of 7DW8-5 were also explored (**16a** and **16b**).



Although many SAR studies have been performed on KRN7000, only a limited SAR study has been done on 7DW8-5. Therefore, structural modifications on the sugar head and sphingoid base of 7DW8-5 were performed to promote a more potent and Th1 skewing response with the goal of developing a promising anti-cancer agent or vaccine adjuvant.

1.2 RESULTS AND DISCUSSION

1.2.1 Research Objectives

The goals of this study were to synthesize the following glycolipid analogs for an improved Th1 biasing NKT cell response

1. α (1-2) Disaccharide of 7DW8-5, **13**
2. Sphinganine/C6'' ester analogs of 7DW8-5, **14a/b**
3. Sphinganine analog of 7DW8-5, **15**
4. C6'' ester analogs of 7DW8-5, **16a/b**

1.2.2 Synthesis of Glycolipid **13**

1.2.2.1 Retrosynthetic Strategy for Glycolipid **13**

The retrosynthetic strategy for **13** is summarized in Figure 2.1. The final target compound can be achieved through a glycosylation between sugar donor **17** and ceramide acceptor **19**. Following the protocol developed by Yanke Liang in the Howell lab, compound **17** was accessible in five steps from purchased tri-O-acetyl galactal (**18**).⁴³ Ceramide **19** could be generated in four steps from commercially available phytosphingosine (**20**) by making minor adjustments to procedures and protecting group strategies used in the Howell group.

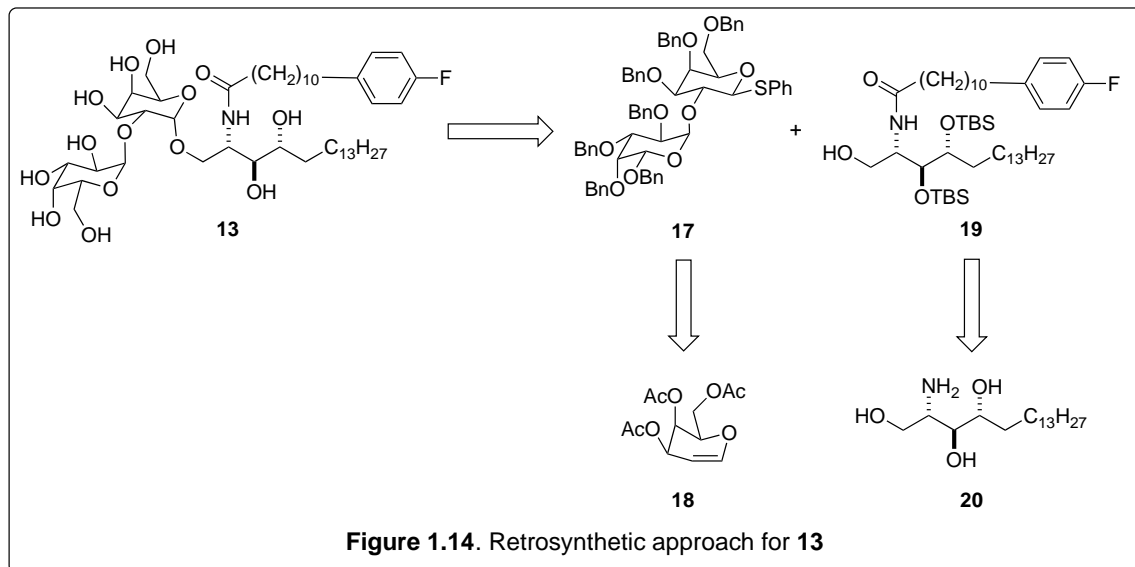


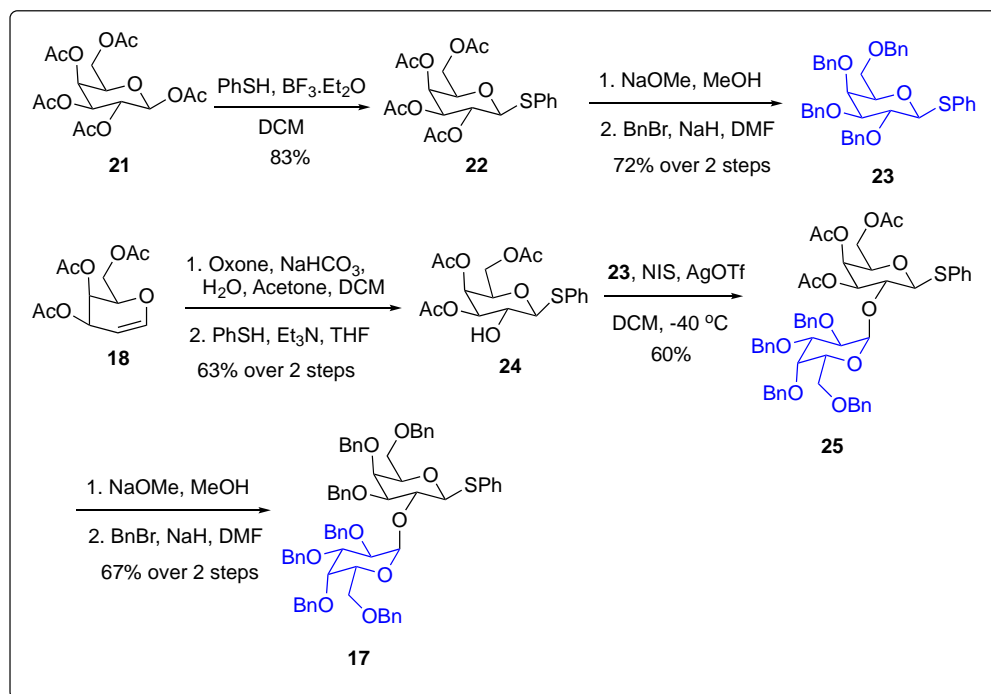
Figure 1.14. Retrosynthetic approach for **13**

1.2.2.2 Synthesis of Sugar Donor **17**

Because the sugar donor (**17**) for **AH15-7** is a disaccharide, two different sugars had to be synthesized and linked. The synthesis of **17** began with a thiophenol substitution on the anomeric acetate of β -D-pentaacetyl galactose **21** in the presence of boron trifluoride diethyl etherate (Scheme 1.1).⁴⁴ The remaining acetates were then cleaved under basic conditions, and the alcohols were protected with benzyl groups using standard methods, giving **23** in 72% yield over two steps. Benzyl-protected sugar **23** is one of the glycosylation partners for **17**. The synthesis of the other monosaccharide (**24**) began with tri-O-acetylgalactal (**18**). The corresponding epoxide was formed by generating dimethyldioxirane (DMDO) *in situ*. Subsequent cleavage by nucleophilic ring opening using thiophenol gave **24** in two steps.⁴⁵ Compounds **23** and **24** were chosen as glycosyl donor and acceptor, respectively, based on the armed/disarmed approach of glycosylations to prevent self-glycosylation. Acetylated sugars are considered disarmed, while benzylated

sugars are armed due to electronic effects (electron withdrawing and donating respectively).⁴⁶ It would be highly unfavorable for an electron-rich sugar to couple with another electron-rich sugar. Therefore, successful glycosylations require one reactant to be electron-donating (glycosyl donor) and the other to be electron-withdrawing (glycosyl acceptor) in order to ensure the most favorable electronic effects. Coupling **23** and **24** using NIS and silver triflate produced disaccharide **25** with no β -disaccharide detected via nuclear magnetic resonance (NMR). Once again, following the armed/disarmed theory, the acetates were cleaved with sodium methoxide in methanol, and the alcohols were then re-protected with benzyls to form armed disaccharide **17**.⁴³

Scheme 1.1. Synthesis of Sugar **17**

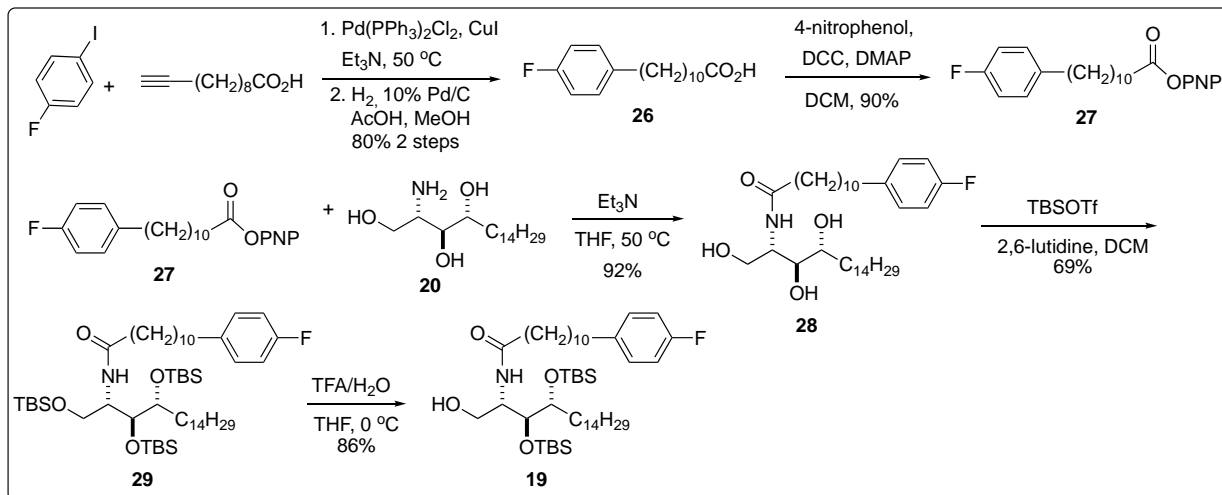


1.2.2.3 Synthesis of Ceramide Acceptor **19**

The synthesis of ceramide acceptor **19** required preparation of the acyl chain for coupling to the sphingoid base. The fatty acyl chain of 7DW8-5 was accessed in three steps

(Scheme 1.2). First, a Sonagashira coupling reaction between 4-fluoroiodobenzene and 10-undecynoic acid resulted in coupled alkyne product, which was then reduced to the alkane (**26**) via hydrogenation with palladium on carbon in 80% yield over two steps.⁴⁷ Although Sonagashira coupling is not a clean reaction and tends to form byproducts, it was found that the overall yield was improved when purification occurred after reducing the alkyne. Therefore, the Sonagashira crude material was filtered through celite to remove the palladium reagent and then carried over to the next step. Activated *p*-nitrophenyl (PNP) ester **27** was prepared in excellent yield through a Steglich esterification using *N,N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).⁴⁸ *N*-acylation was performed on phytosphingosine (**20**) with **27** under mildly basic conditions with consistently excellent yields. All alcohols were then protected with TBS, and the primary alcohol in **29** was selectively de-protected using TFA in water to access **19** in 80% yield.⁴³

Scheme 1.2. Synthesis of Ceramide Acceptor



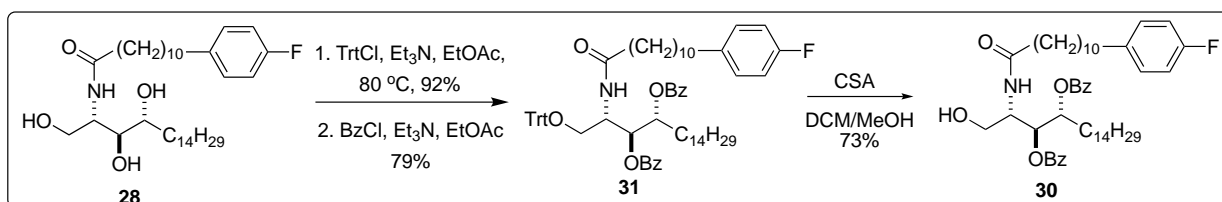
1.2.2.4 Glycosylation and Final Steps for **AH15-7**

Unfortunately, the glycosylation between ceramide acceptor **19** and glycosyl donor **17** was low yielding with very poor $\alpha:\beta$ selectivity. This result was thought to be due to electronic effects mentioned previously in the armed/disarmed theory. Silyl ethers are not good electron-withdrawing groups to promote a favorable glycosylation. As a result, the protecting group strategy had to be modified to promote good electronic effects.

In the first reported synthesis of 7DW8-5 by Wong and co workers, they performed the glycosylation between a benzoyl- and Boc-protected phytosphingosine to great success. This strategy was chosen so that they could incorporate different acyl chains in a final step. Following their lead, it was decided that protecting the alcohols of the ceramide with benzoyls would provide adequate electron withdrawing effects to promote a successful glycosylation. Typically, this method is done first by selectively protecting the primary alcohol with a bulky trityl protecting group, then protecting the secondary alcohols with benzoyls. Under acidic conditions, the trityl can be cleaved while the ester protecting group (Bz) remain. Both protection reactions are primarily performed under basic conditions using DMAP and pyridine.⁴⁹ However, when this strategy was attempted with **28**, both reactions were low yielding and inconsistent. Therefore, following a different method, the reactions were slightly modified by using a different base and solvent (**31** in Scheme 1.3).⁵⁰ The combination of triethylamine (Et₃N) and ethyl acetate (EtOAc), seemed to improve the reaction slightly, but once again, the results were inconsistent. Eventually it was observed through crude NMR analysis, that trityl protection was proceeding with 100% conversion. When subjected to column chromatography however, only starting material was isolated. Therefore, it was concluded that the trityl group was

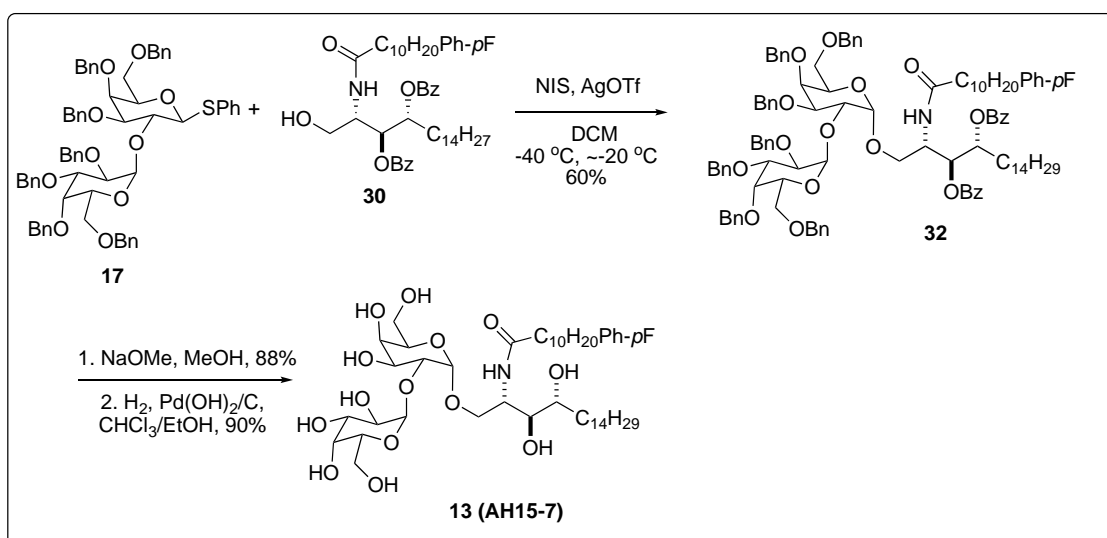
cleaved during purification due to the slightly acidic nature of silica gel in column chromatography. This problem was overcome by neutralizing the column prior to loading the crude material. Then, the reactions resulted in significantly higher isolated yields with more consistent success. Finally using 10-camphorsulfonic acid (CSA), the trityl group was cleaved while maintaining secondary alcohol protection to achieve ceramide acceptor **30** in 73% yield.⁵⁰

Scheme 1.3. Modified Protecting Group Strategy



With both ceramide and sugar in hand, the final glycosylation could be performed Using NIS/AgOTf as the activator and methylene chloride as the solvent, protected glycolipid **32** was achieved in 60% yield with no β -isomer detected (Scheme 1.4). Finally, the benzoyl protecting groups were cleaved using sodium methoxide in 88% yield. Hydrogenolysis provided **AH15-7** in 90% yield.

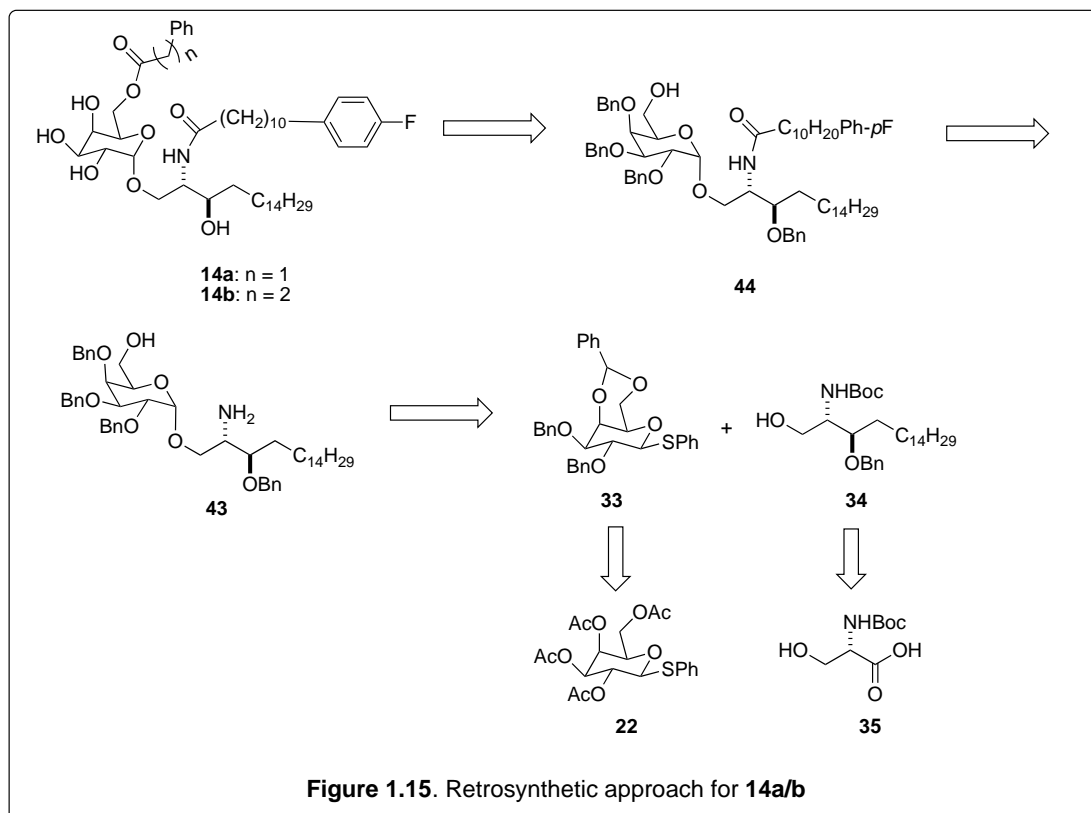
Scheme 1.4. Final Steps in the Synthesis of **AH15-7**



1.2.3 Synthesis of C6'' Ester Analogs 14a and 14b

1.2.3.1 Retrosynthetic Strategy for Glycolipids 14a/b

The retrosynthetic approach for the sphinganine-containing C6'' ester analogs of 7DW8-5 is summarized in Figure 1.15. Glycosylation was planned between a sugar donor (**33**) and sphingoid base acceptor **34**. Although glycosylation with a ceramide acceptor was shown to work very well previously (Scheme 1.4), the glycosylation had to be performed with the sphingoid base for these analogs in order to cleave the benzylidene protecting group after glycosylation. Intermediate **43** is a result of cleaving both the benzylidene and Boc protecting groups in one step. Following a method reported by the Howell group, sphingoid base acceptor **34** can be achieved in six steps from commercially available Boc-L-serine (**35**). Benzylidene-protected sugar **33** can be accessed from **22** (see Scheme 1.1) in three steps through a known procedure. This sugar was chosen for

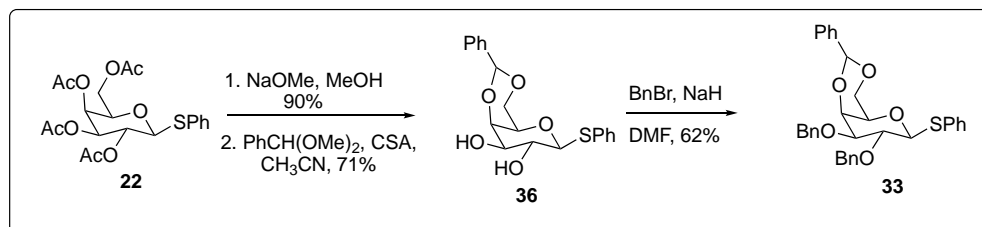


glycosylation for late-stage installation of structural diversity at the C6'' alcohol. The goal was to protect the C6'' alcohol for as long as possible for a divergent synthesis of the C6'' ester analogs. Therefore, only one glycosylation would have to be performed, and the material could be split in half for two analogs. Sugar **33** is also a beneficial intermediate, because the 4,6-benzylidene protecting group has been extensively studied and methods have been developed for selectively cleaving it to expose the C4'' or C6'' alcohol. As a result, the benzylidene protected sugar was chosen to take advantage of the high C4'' versus C6'' selectivity and the ability to generate analogs late in the synthesis.

1.2.3.2 Synthesis of Sugar Donor **33**

The synthesis of donor **33** began with thiophenyl sugar **22** (Scheme 1.5). Upon treatment with sodium methoxide in methanol, the acetate protecting groups were cleaved. The C4'' and C6'' hydroxyls were subsequently protected with benzaldehyde dimethyl acetal (**36**). The two remaining alcohols were protected with benzyls to achieve benzylidene-modified benzyl-protected sugar **33** with good yields.⁵¹ The synthesis of **33** was performed on a large scale (>20 g) by Dr. Divya Chennamadhavuni of the Howell lab, and the compound was shared with the group members.⁵²

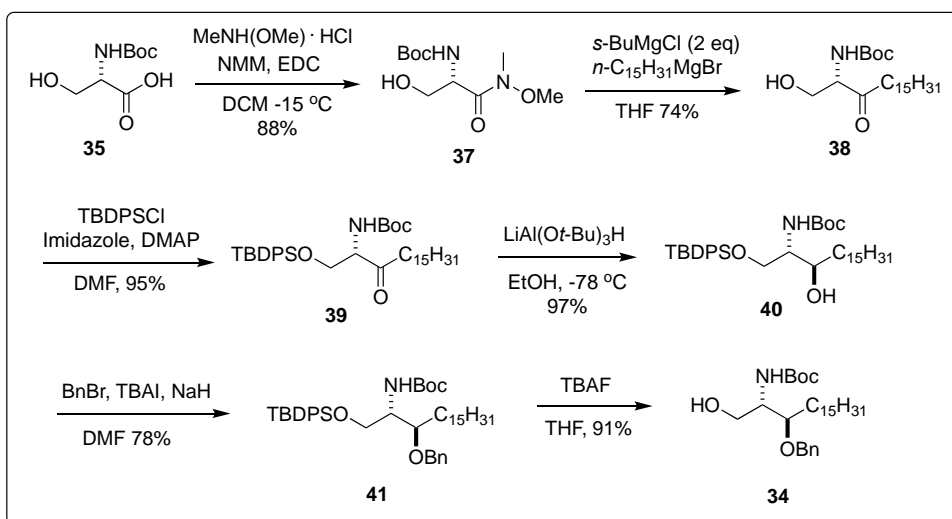
Scheme 1.5. Synthesis of Sugar Donor for **AH17-2** and **AH17-3**



1.2.3.3 Synthesis of Sphingoid Base **34**

The first step towards accessing **33** involves converting Boc-L-serine (**35**) to the corresponding Weinreb amide **37** (Scheme 1.6). Double deprotonation of **37** using two equivalents of isopropylmagnesium chloride as a sacrificial base allowed for a Grignard reaction using pentadecylmagnesium bromide to generate ketone **38** in 74% yield. Pentadecylmagnesium bromide was generated by combining 1-bromopentadecane with magnesium turnings in refluxing tetrahydrofuran (THF). Protection of the primary alcohol in **38** with *tert*-butyldiphenylsilyl chloride (TBDPSCI) gave **39** in 95% yield. The ketone then underwent diastereoselective reduction using lithium tri-*tert*-butoxyaluminum hydride to provide the secondary alcohol (**40**) in 97% yield. The reaction is clean, rarely requires purification, and the other diastereomer was never observed. Alcohol **40** was then protected using sodium hydride and benzyl bromide (**41**). The primary alcohol was selectively de-protected upon treatment with tetrabutylammonium iodide (TBAF) in THF, giving **34** in 91% yield.²⁸

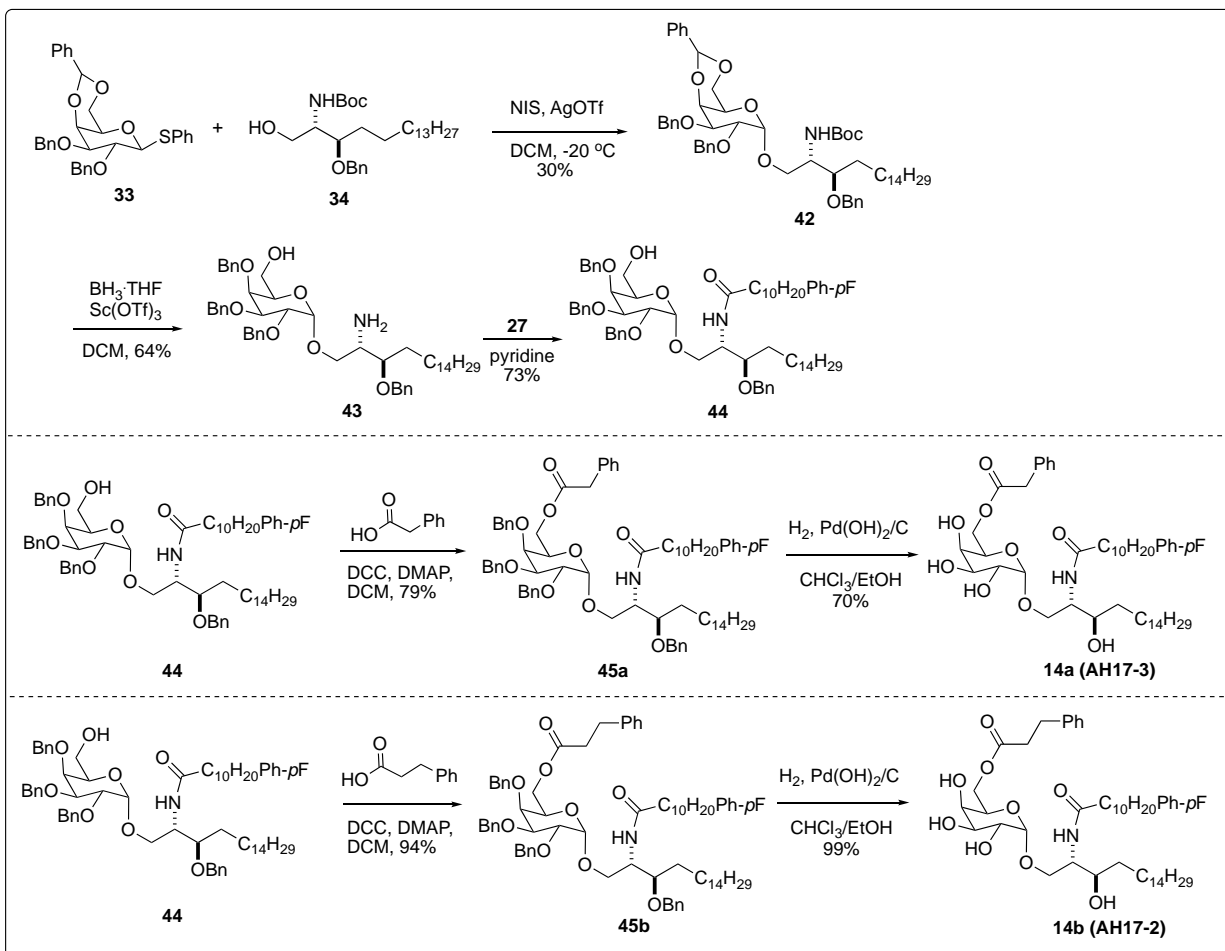
Scheme 1.6. Synthesis of sphingoid base acceptor **34**



1.2.3.4 Glycosylation and Final Steps for The Synthesis of **AH17-2** and **AH17-3**

Compounds **33** and **34** were coupled under the established conditions (Scheme 1.7). Unfortunately, with a sphingoid base instead of a ceramide, the yield was low, and α/β selectivity was only 1:1. The α isomer was isolated in 20% yield and carried forward. Using 1M borane-tetrahydrofuran complex and scandium triflate, the benzylidene was selectively cleaved on the C6'' alcohol.⁵³ Under these conditions, the Boc protecting group was also cleaved (**42**). For this reason, the glycosylation had to be performed on the sphingoid base. It was observed in a previous attempt that the reaction conditions not

Scheme 1.7. Synthesis of **AH17-2** and **AH17-3**

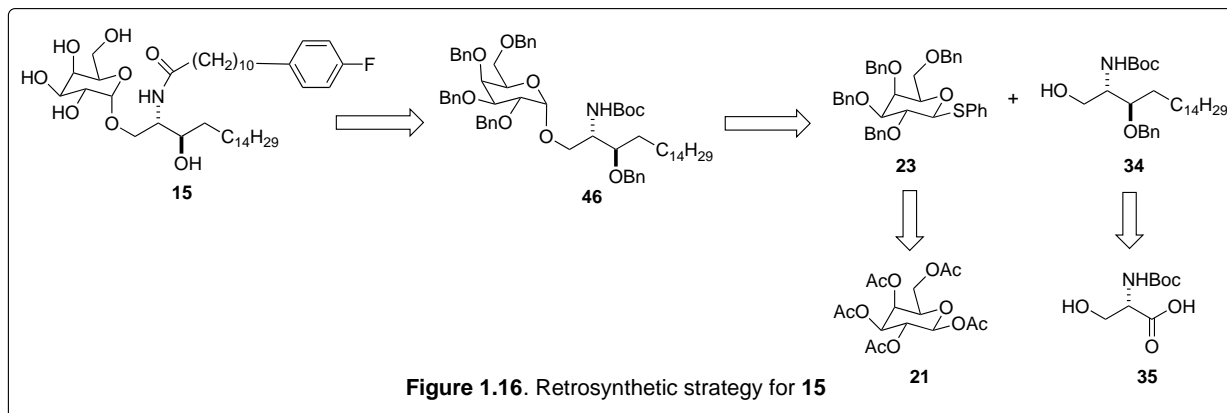


only cleaved carbamates and acetals, but also amide bonds. Therefore, when glycosylation occurred on the ceramide acceptor, the acyl chain was also removed when the benzylidene cleaving reaction was run. Armed with this knowledge, the synthetic strategy utilized the reaction conditions to expose both the C6'' alcohol and C2 amine. *N*-acylation with **27** was performed under basic conditions to access **44** in 73% yield. Because amines are much more nucleophilic than alcohols, there was no concern over esterification of the C6'' alcohol. With only a few steps left, **44** was split into two aliquots to generate the two target glycolipids. Upon esterification with phenylacetic acid under Steglich conditions, **45a** was formed in 79% yield, and global deprotection using Pearlman's catalyst gave **AH17-3** in 70% yield. Starting at **44** again, Steglich esterification using hydrocinnamic acid gave **45b** in 94% yield. Finally, cleavage of the benzyls gave **AH17-2** in 99% yield.

1.2.4 Synthesis of Sphinganine Analog of 7DW85 (15)

1.2.4.1 Retrosynthetic Strategy for **AH17-1**

Because the synthesis of **AH17-1** was occurring at the same time as **AH17-2** and **AH17-3**, it was simpler to perform the glycosylation on sphingoid base **34** and sugar **23** due to the availability of these advanced intermediates in the lab (Figure 1.16). The synthesis of both **23** and **34** have been described previously (Schemes 1.1 and 1.6, respectively).

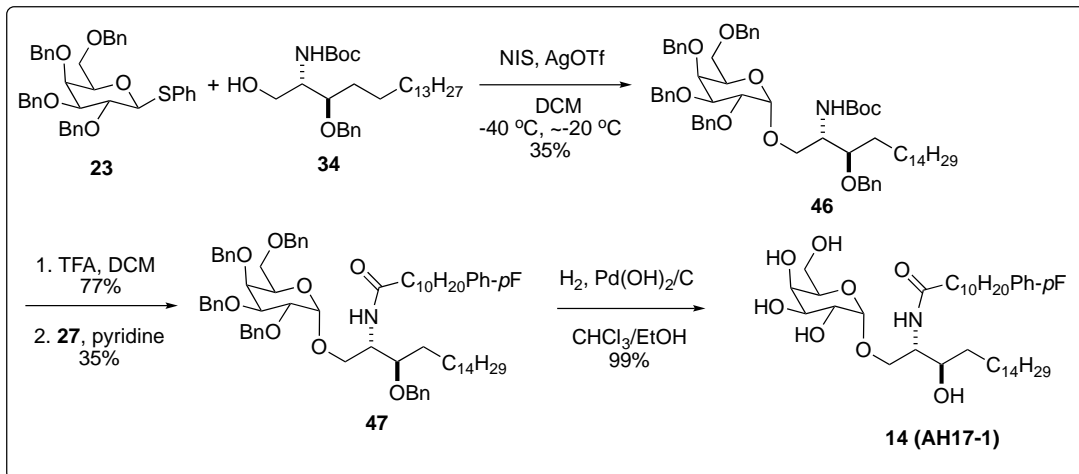


1.2.4.2 Glycosylation and Final Steps Towards **AH17-1**

Glycosylation of sphingoid base **34** with **23** was performed under the same conditions described previously. Similar to the former glycosylations with a sphingoid base, the yield was moderate with a 2:1 α/β ratio. This result is most likely due to electronic effects from protecting groups (benzyl-protected alcohol on the sphingoid base). The α isomer was isolated in 35% yield and carried forward (**46** in Scheme 1.8). Boc-amine **46** was deprotected using TFA to access the free amine in 77% yield. In the presence of pyridine, the amine underwent *N*-acylation with PNP ester **27** (see Scheme 1.2) to yield glycoside **47**. *N*-Acylation reactions continue to be an ongoing problem in the lab when the previous reaction is cleaving Boc with trifluoroacetic acid (TFA). One thought as to why the reaction is low yielding is due to pH effects. The reaction with TFA is acidic, and the work up involves neutralizing the crude material with a base (aqueous sodium bicarbonate). If the reaction is not properly neutralized prior to the next step, the reaction may not proceed. Interestingly, it was found that when Boc was cleaved under milder conditions and the crude material was purified via column chromatography (**23** in Scheme 1.7), *N*-acylation proceeded with good to excellent yields. That method however, was not performed on **46**

to achieve **47**. Global de-protection was accomplished by hydrogenolysis, providing **AH17-1** in 99% yield.

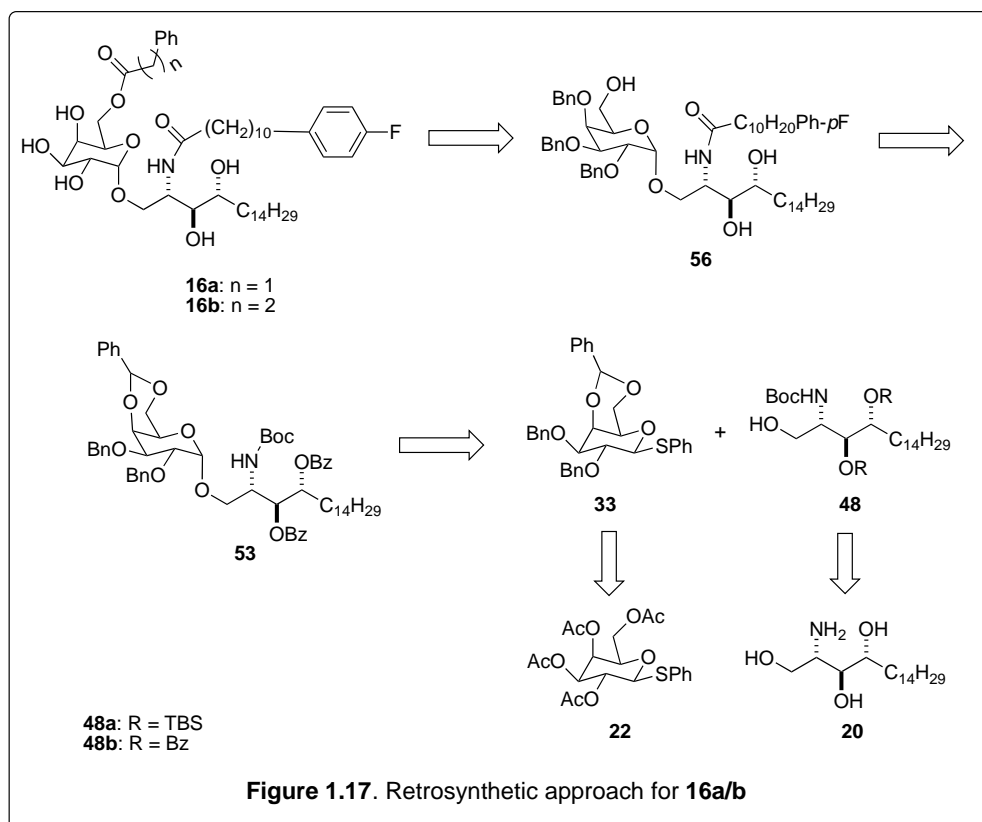
Scheme 1.8. Synthesis of **AH17-1**



1.2.5 Synthesis of C6'' Ester Analogs of 7DW8-5 (**16a** and **16b**)

1.2.5.1 Retrosynthetic Approach to **16a** and **16b**

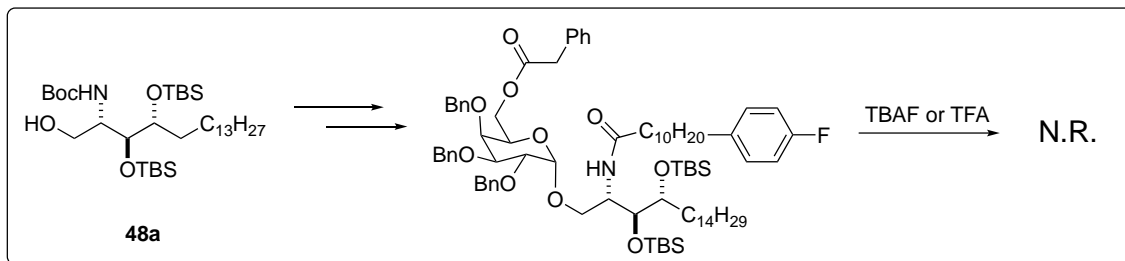
The plan was to prepare targets **16a** and **16b** in the same manner as the other C6'' esters (**14a** and **14b**) with a glycosylation between **33** and protected phytosphingosine **48** (Fig. 1.17). The synthesis of sugar donor **33** was described in Scheme 1.5. Sphingoid base **48** can be accessed in five steps from phytosphingosine (**20**) by following literature procedures. Once again, structural diversity at the C6'' position is installed after glycosylation.



1.2.5.2 Synthesis of Glycosyl Acceptor **48**

When looking at which protecting group strategy should be employed for **48**, the entire glycolipid synthesis had to be considered. Although benzoyl protecting groups would ensure good electronic effects for glycosylation (**48b**), they are esters and would have to be removed prior to esterification of the C6'' alcohol. TBS protecting groups resulted in poor glycosylation results in section 1.2.2.4, however, they can usually be cleaved in acidic conditions which won't affect the C6'' ester (**48a**). For this reason, **48a** was chosen as the glycosyl acceptor. Unfortunately, in one of the last steps of the synthesis when the TBS groups had to be removed, no reaction was observed (Scheme 1.9). When both TBAF and TFA methods were employed, only starting material was recovered even when the reaction was allowed to run for days with high equivalents of the cleaving reagent.

Scheme 1.9. Failed synthetic strategy involving **48a**



Therefore, it was determined that the benzoyl-protection was the best route. When looking at **48b**, it was tempting to perform the same protecting group strategy used in Scheme 1.3 where the primary alcohol was protected with trityl and the secondary alcohols were protected with benzoyls. Subsequent selective de-protection of the primary alcohol and protection of the free amine would give the desired sphingoid base. This protecting group strategy resulted in the greatest glycosylation yield and α -selectivity (**AH 15-7**). Encouraged by the previous success, the Trt/Bz protecting group strategy was employed. Unfortunately, the sphingoid base synthesis was not as straightforward as anticipated. First, the free amine in phytosphingosine was protected with Boc under standard conditions without purification required (**49**). Trityl protection was attempted under the conditions shown in Scheme 1.3 with Et₃N and EtOAc. No product was isolated, and only starting material was recovered (Scheme 1.10a). This result was thought to be due to solubility issues; while ceramide **28** was soluble in EtOAc, sphingoid base **49** was not. Therefore, another trityl protection method was employed with DMAP and pyridine.⁴⁹ Although the average yield for this reaction was low, the material was carried forward with benzoyl protections. As noted, the trityl group can be and was cleaved serendipitously during purification on the mildly acidic column (**48b**). Once again, the average yield was too low to establish this method as a reliable way to make the desired sphingoid base

a.

b.

c.

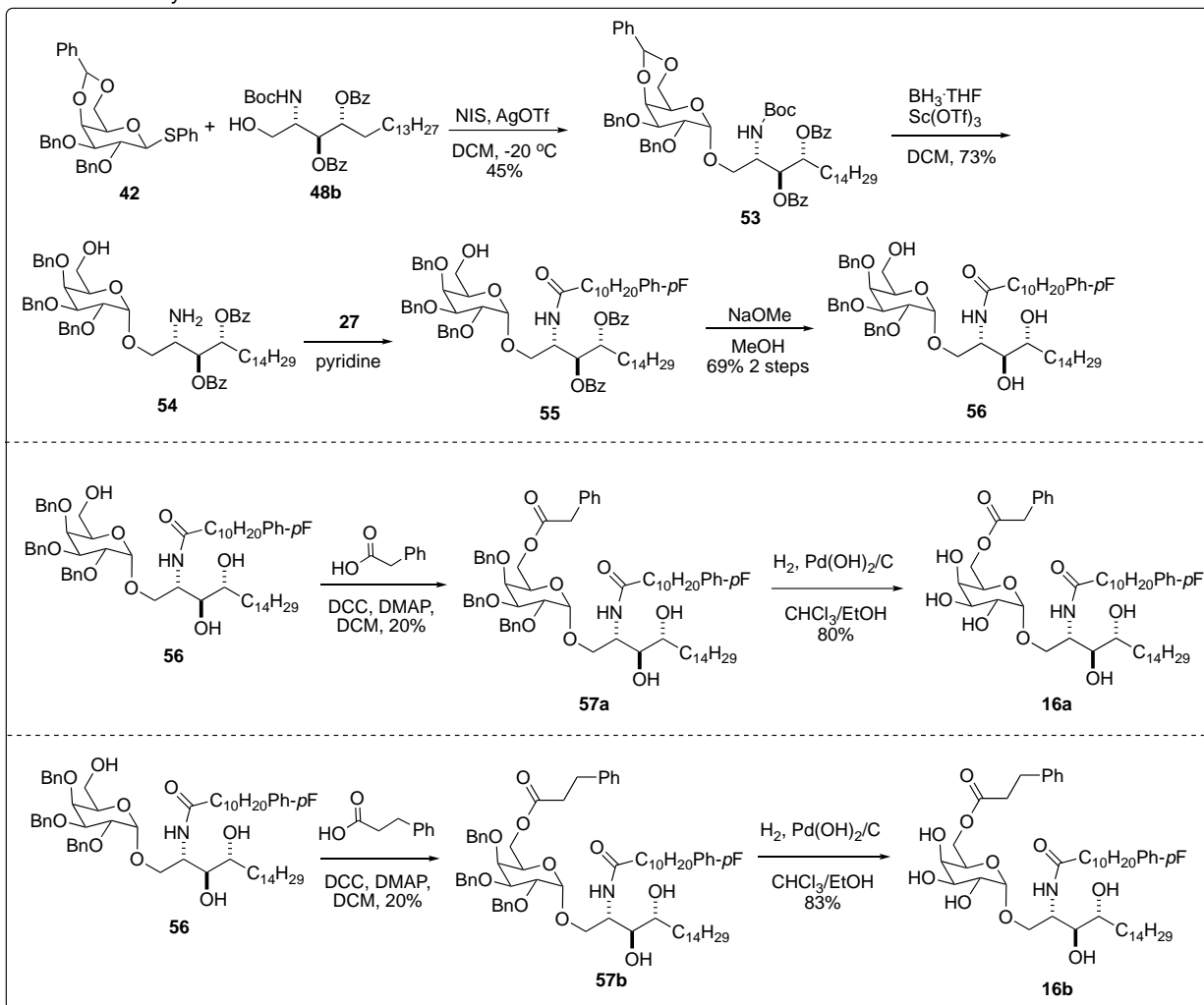
d.

37

1.2.5.3 Glycosylation and Final Synthesis of **16a** and **16b**

The final steps for **16a** and **16b** are similar to Scheme 1.8 with slight differences to account for the phytosphingosine base (Scheme 1.11). The standard glycosylation between **42** and **48b** resulted in glycoside **53** with a good yield in terms of glycosylation reactions. The benzylidene and Boc were cleaved using boron tetrahydrofuran complex and scandium triflate to expose the C6'' alcohol and C2 amine (**54**). *N*-acylation with **27** resulted in glycolipid **55**. For this reaction sequence, the benzoyl protecting groups had to be removed prior to esterification at C6'' (**56**). Benzoyl protecting groups are also esters; therefore, the conditions required to cleave benzoyl, would also cleave the newly installed C6'' ester. Once again, the glycolipid preceding esterification was split into two portions for Steglich esterifications with phenylacetic acid and hydrocinnamic acid (**57a** and **57b**, respectively). Both esterifications were low yielding, which was thought to be due to the two secondary alcohols available for esterification. Although the primary alcohol is the most available sterically, in both reactions, column purification resulted in product, impure unreacted starting material, and doubly esterified glycolipids. This step was the reason why the TBS-protecting group strategy was chosen first in order to prevent esterification at the secondary alcohols. However as mentioned in section 1.2.5.2, the TBS groups caused problems later in the synthesis that made it impossible to continue. Hydrogenation of **57a** and **57b** resulted in the final C6'' ester-modified analogs of 7DW8-5, **16a** and **16b**.

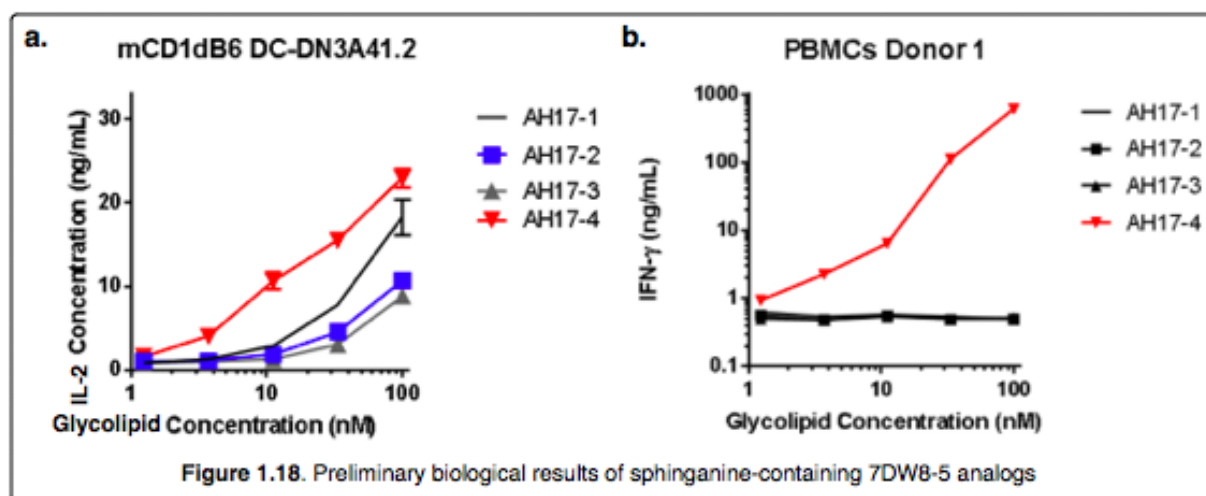
Scheme 1.11. Synthesis of **16a** and **16b**



1.2.6 Preliminary Biological Results

All six glycolipids have been sent to the Albert Einstein School of Medicine for biological testing. Of the glycolipids sent, AH17-1, AH17-2, and AH17-3 have been tested with murine CD1d in B6 cells. IL-2 production was measured 24 hours after addition of the glycolipid solution at varying concentrations (Fig. 1.18a). These compounds are the sphinganine analogs of 7DW8-5 with and without C6" esters. AH17-4 is 7DW8-5 that has been synthesized in the Howell lab. When comparing the sphinganine-containing compounds' activities to 7DW8-5, all three analogs are less potent. In Figure 1.18b, the

glycolipids were examined in human peripheral blood mononuclear cells (PMBCs). Once again, all analogs were less potent than 7DW8-5. This result is thought to be partially due to solubility problems. Because **AH17-2** and **AH17-3** have two fewer alcohols than 7DW8-5, they are less polar and therefore don't dissolve in water or DMSO as well. These compounds are being tested in aqueous, cellular environments; therefore, water solubility is essential. **AH17-1** is more active than the C6" esters but still less potent than 7DW8-5. Because **AH17-1** is only lacking one alcohol in comparison to 7DW8-5, it is more soluble in water than the C6" esters, which could explain the higher potency. It's important to note, however, that although these trends could be partially due to solubility, it doesn't give any insight into how the glycolipids are interacting with CD1d or NKT cells, which is much more difficult to elucidate. As mentioned, these compounds are in the preliminary stage of testing, and one result alone is not indicative of a compound's activity. Although these results don't seem promising, the phytosphingosine-containing analogs have not been tested yet and are anticipated to perform better. Further studies are currently being performed in Dr. Steven Porcelli's lab at Albert Einstein School of Medicine.



1.2.7 Conclusions

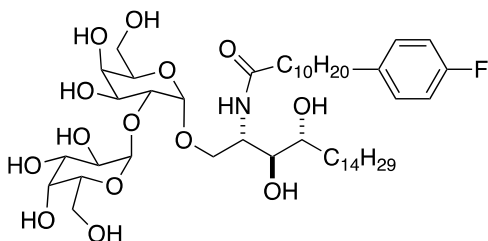
Six analogs of 7DW8-5 have been reported for the purpose of activating λ NKT cells for Th1 cytokine production. The structural modifications performed on 7DW8-5 were selected based on alterations done to KRN7000 that was shown to skew towards a Th1 response. Although initial biological testing showed very little activity in analogs **AH17-1**, **AH17-2**, and **AH17-3**, these compounds are in the very early stage of examination. The remaining analogs presented have not yet been investigated for their biological activity.

1.3 EXPERIMENTAL

General experimental. Methylene chloride (DCM), dimethylformamide (DMF), pyridine, chloroform (CHCl_3) and toluene were dried over CaH_2 . THF was purified by a J. C. Myer Solvent Dispensing system. All reactions, unless specified, were conducted under an atmosphere of N_2 . Where appropriate, control of temperature was achieved with a solid CO_2 /acetone bath, a Cryocool CC-100 II immersion cooler, an ice-bath or a heated oil bath. Phytosphingosine was purchased from Evonik, and β -D-galactose pentaacetate was purchased from Carbosynth. All other commercially available reagents were purchased from Sigma-Aldrich, Acros, TCI Alfa-Aesar or Oakwood.

^1H NMR spectra were recorded at 400 MHz and/or at 500 MHz and calibrated to the residual CHCl_3 peak at 7.26 ppm. The following abbreviations are used for peak multiplicities: br s (broad singlet), s (singlet); d (doublet); t (triplet); q (quartet); quintet (quin); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets). ^{13}C NMR spectra were recorded at 100MHz and/or at 125 MHz and calibrated to the CDCl_3 peak at 77.23 ppm. Chemical shifts are reported in units of parts per million (ppm). Coupling constants, J , are reported in Hertz (Hz). Infrared (IR) spectra were recorded on an FT-IR spectrophotometer and are reported in cm^{-1} . High-resolution mass spectra were obtained on an AccuESI instrument at the University of Connecticut. Specific rotations $[\alpha]_D$ were obtained on a JASCO P-2000 polarimeter, using the sodium D-line as a source, and the concentration (c) is expressed in g per 100 mL. Flash chromatography was performed on Silica Gel, 40 microns, 32-63 flash silica. Thin layer

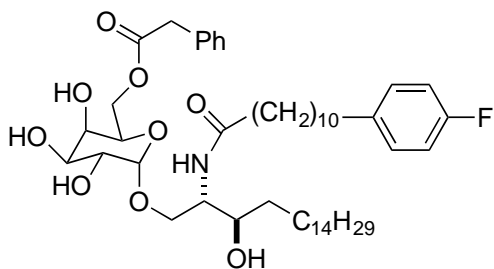
chromatography was performed on silica gel (Silica Gel 60 F₂₅₄) glass plates, and the compounds were visualized by UV and/or 5% phosphomolybdic acid in ethanol.



(2*S*,3*S*,4*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-*O*-[2-*O*-(α-*D*-galactopyranosyl)-α-*D*-galactopyranosyl]octadecan-1,3,4-triol (13**)**

(2*S*,3*S*,4*R*)-2-Amino-1-*O*-[2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-*D*-galactopyranosyl]-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (**32**) (0.035 g, 0.027 mmol) was dissolved in MeOH/CHCl₃ (v/v 1:4, 2.2 mL) under N₂. Pd(OH)₂/C (0.134 g) was added, and the reaction vessel was purged with H₂. The reaction mixture was stirred for 5 h under a H₂ balloon. It was then filtered through celite, and the celite pad was rinsed with MeOH/CHCl₃ (v/v 1:1, 10 mL). The filtrate was concentrated, and the crude product purified via flash column chromatography on silica gel (DCM/MeOH 80:20) to give **13** as a white film (0.022 g, 90%): [α]_D²⁵ +83 (*c* 0.05, MeOH); IR (neat) 3330 (br), 2923, 2853, 1510, 1070 cm⁻¹; ¹H NMR (400 MHz, MeOD/CDCl₃) δ 7.13 (m, 2H), 6.94 (m, 2H), 5.03 (d, *J* = 3.0 Hz, 1H), 5.02 (d, *J* = 2.8 Hz, 1H), 4.15 (m, 2H), 3.93 (m, 3H), 3.86–3.70 (m, 10H), 3.59 (m, 1H), 3.39 (m, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.23 (t, *J* = 7.6 Hz, 2H), 1.60 (m, 6H), 1.27 (m, 34H), 0.89 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.1, 160.8 (*d*_{C-F}, *J* = 240.9 Hz), 138.1 (*d*_{C-F}, *J* = 2.9

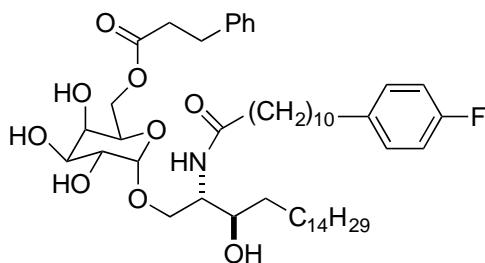
Hz), 129.2 (d_{C-F}, *J* = 7.6 Hz), 114.3 (d_{C-F}, *J* = 20.9 Hz), 97.5, 97.0, 74.7, 73.6, 71.7, 70.7, 70.3, 69.7, 69.6, 69.4, 68.5, 68.1, 67.0, 61.6, 61.2, 49.8, 35.8, 34.6, 31.5, 31.2, 31.1, 29.3, 29.2, 29.2, 29.1, 29.1, 29.0, 28.9, 28.7, 25.6, 25.5, 22.1, 13.2; HRMS (ESI) for C₄₇H₈₃FNO₁₄ (M + H)⁺ *m/z* calcd: 904.5798. Found: 904.5763.



(2*S*,3*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-*O*-(6-*O*-phenylacetoyl- α -D-galactopyranosyl)octadecan-1,3-diol (14a**)**

(2*S*,3*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl-6-phenyl-acetoyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3-diol (**45a**) (0.008 g, 0.007 mmol) was dissolved in CHCl₃/MeOH (1:4 v/v, 0.5 mL) under N₂. Pd(OH)₂/C (0.010 g) was added, and the reaction vessel was purged with H₂. The reaction mixture was stirred overnight under a H₂ balloon. The reaction mixture was diluted with MeOH (2 mL) and CHCl₃ (1 mL) then filtered through celite. The celite was rinsed with MeOH and DCM (1:5 v/v, 10 mL). The crude product was purified via flash column chromatography on silica gel (DCM/MeOH 95:5) to give **14a** as a white film (0.004 g, 70%): [α]_D²⁵ –45 (*c* 0.04, DCM); IR (neat) 3370 (br), 2922, 2852, 1734, 1645 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (m, 4H), 7.11 (m, 3H), 6.95 (m, 2H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.24 (d, *J* =

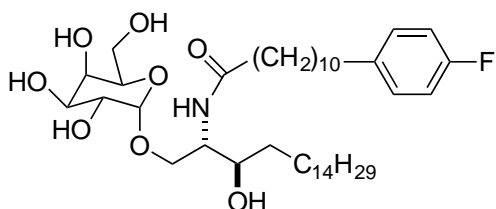
8.2 Hz, 1H), 4.88 (d, $J = 3.6$ Hz, 1H), 4.41 (dd, $J = 11.6, 6.2$ Hz, 1H), 4.21 (dd, $J = 11.5, 7.0$ Hz, 1H), 4.10 (m, 1H), 4.00 (m, 1H), 3.93–3.73 (m, 5H), 3.59 (dd, $J = 10.6, 4.6$ Hz, 1H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.96–2.56 (br, 4H), 2.21 (m, 2H), 1.57 (m, 6H), 1.26 (m, 40H), 0.88 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 171.8, 161.2 ($\text{d}_{\text{C-F}}$, $J = 254.6$ Hz), 138.4 ($\text{d}_{\text{C-F}}$, $J = 8.6$ Hz), 129.6 ($\text{d}_{\text{C-F}}$, $J = 7.7$ Hz), 129.3, 128.7, 127.8, 127.3, 114.9 ($\text{d}_{\text{C-F}}$, $J = 20.9$ Hz), 113.9, 99.8, 73.3, 70.5, 69.2, 68.9, 68.7, 68.3, 63.3, 52.3, 41.2, 37.4, 37.1, 36.9, 35.1, 34.7, 32.8, 31.9, 31.6, 30.0, 29.7, 29.6, 29.5, 29.4, 29.2, 27.4, 27.1, 26.7, 26.0, 25.8, 25.5, 24.5, 22.7, 19.7, 14.1; HRMS (ESI) for $\text{C}_{49}\text{H}_{79}\text{FNO}_9$ ($\text{M} + \text{H}$) $^+$ m/z . calcd: 844.5741. Found: 844.5771.



(2*S*,3*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-*O*-(6-*O*-hydrocinnamoyl)- α -D-galactopyranosyl)octadecan-1,3-diol (14b**)**

(2*S*,3*R*)-2-Amino-(2,3,4-tri-*O*-benzyl-6-hydrocinnamoyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3-diol (**45b**) (0.008 g, 0.007 mmol) was dissolved in $\text{CHCl}_3/\text{MeOH}$ (1:4 v/v, 0.5 mL) under N_2 . $\text{Pd}(\text{OH})_2/\text{C}$ (0.010 g) was added, and the reaction vessel was purged with H_2 . The reaction mixture was stirred overnight under a H_2 balloon. It was then diluted with MeOH (2 mL) and CHCl_3 (1 mL) and filtered through celite. The celite was rinsed with MeOH and DCM (1:5 v/v, 10 mL). The filtrate was concentrated, and the crude product was purified via flash column

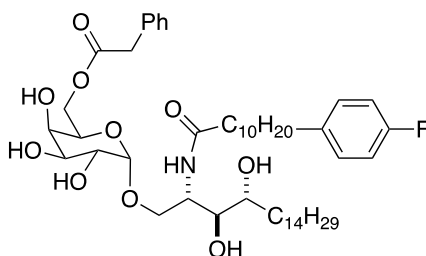
chromatography on silica gel (DCM/MeOH 95:5) to give **14b** as a white film (0.006 g, 99%): $[\alpha]^{25}_{\text{D}} -30$ (c 0.08, DCM); IR (neat) 3353 (br), 2923, 2853 1737, 1639 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.16 (m, 2H), 7.11 (m, 3H), 7.00 (m, 2H), 6.94 (m, 2H), 6.70 (d, $J = 8.2$ Hz, 1H), 4.73 (d, $J = 3.7$ Hz, 1H), 4.13 (m, 1H), 3.97 (m, 1H), 3.80 (m, 2H), 3.66 (m, 1H), 3.60 (dd, $J = 10.0, 3.3$ Hz, 1H), 3.56 (m, 3H), 3.47 (m, 1H), 2.83 (t, $J = 7.7$ Hz, 2H), 2.55 (t, $J = 7.8$ Hz, 2H), 2.45 (t, $J = 7.5$ Hz, 2H), 2.09 (t, $J = 7.0$ Hz, 2H), 1.50–1.30 (m, 8H), 1.25 (m, 36 H), 0.88 (t $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.2, 173.2, 161.1 ($\text{d}_{\text{C-F}}$, $J = 243.0$ Hz), 140.2, 138.5 ($\text{d}_{\text{C-F}}$, $J = 3.0$ Hz), 129.6 ($\text{d}_{\text{C-F}}$, $J = 7.7$ Hz), 128.5, 128.2, 126.3, 114.8 ($\text{d}_{\text{C-F}}$, $J = 21.0$ Hz), 99.7, 71.6, 70.2, 70.0, 69.1, 68.9, 68.8, 68.5, 68.5, 67.7, 63.6, 53.2, 41.7, 36.5, 35.7, 35.1, 34.1, 31.9, 31.6, 30.9, 30.8, 29.7, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 25.9, 25.8, 22.6, 14.0; HRMS (ESI) for $\text{C}_{50}\text{H}_{81}\text{FNO}_9$ ($\text{M} + \text{H}$) $^+$ m/z . calcd: 858.5895. Found: 858.5914.



(2S,3R)-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-(α -D-galactopyranosyl)octadecan-1,3-diol (15**)**

(2S,3R)-2-Amino-1-(2,3,4,6-tetra-*O*-benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3-diol (**47**) (0.008 g, 0.008 mmol) was dissolved in $\text{CHCl}_3/\text{MeOH}$ (1:4 v/v, 1.0 mL) under N_2 . $\text{Pd}(\text{OH})_2/\text{C}$ (0.010 g) was added, and the reaction vessel was purged with H_2 . The reaction mixture was stirred overnight under a

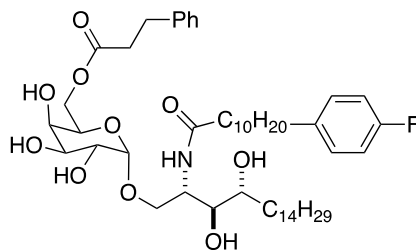
H₂ balloon. It was then diluted with MeOH (2 mL) and CHCl₃ (1 mL) and filtered through celite. The celite was rinsed with MeOH and DCM (1:5 v/v, 10 mL). The filtrate was concentrated, and the crude product was purified via flash column chromatography on silica gel (DCM/MeOH 90:10) to give **15** as a white film (0.005 g, 100%): [α]²¹_D +70 (c 0.1, 1:1 v/v DCM/MeOH); IR (neat) 3304 (br), 2920, 1751 cm⁻¹; ¹H NMR (500 MHz, CDCl₃/MeOD) δ 7.33 (d, *J* = 8.8 Hz, 1H), 6.76 (m, 2H), 6.57 (m, 2H), 4.50 (d, *J* = 3.7 Hz, 1H), 3.55 (m, 2H), 3.55 (m, 1H), 3.44–3.42 (m, 3H), 3.40–3.37 (m, 4H), 3.24 (m, 1H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.85 (t, *J* = 7.5 Hz, 2H), 1.22 (m, 6H), 0.90 (m, 38H), 0.51 (t, *J* = 6.5 Hz, 3H); ¹³C NMR (125 MHz CDCl₃, MeOD) δ 174.4, 160.8 (d_{C-F}, *J* = 241.0 Hz), 138.0 (d_{C-F}, *J* = 3.8 Hz), 129.2 (d_{C-F}, *J* = 7.8 Hz), 114.2 (d_{C-F}, *J* = 21.3 Hz), 99.5, 70.5, 70.3, 69.8, 69.3, 68.6, 67.2, 61.2, 53.5, 35.9, 34.6, 33.5, 31.4, 31.2, 29.2, 29.1, 29.1, 29.1, 29.0, 28.9, 28.8, 28.7, 25.5, 25.2, 22.1, 13.2; HRMS (ESI) for C₄₁H₇₃FNO₈ (M + H)⁺ *m/z*. calcd: 726.5320. Found: 726.5346.



(2S,3S,4R)-2-Amino-N-(11-(4-fluorophenyl)undecanoyl)-1-O-(6-O-phenylacetoyl- α -D-galactopyranosyl)octadecan-1,3,4-triol (16a**)**

(2S,3S,4R)-2-Amino-1-(2,3,4-tri-O-benzyl-6-phenylacetoyl- α -D-galactopyranosyl)-N-(11-(4-fluorophenyl)undecanoyl)octadecan-3,4-diol (**57a**) (7 mg, 0.006 mmol) was dissolved in EtOH/CHCl₃ (4:1 v/v, 0.5 mL) and purged with N₂ under stirring. Pd(OH)₂/C (50 mg)

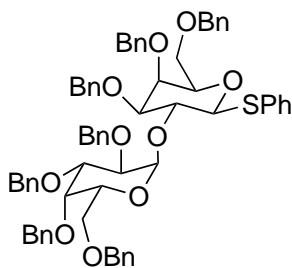
was added, and the reaction vessel was purged with H₂. The reaction mixture was stirred overnight under a H₂ balloon. It was then flushed with N₂ and filtered through celite. The celite pad was rinsed with DCM (5 mL) and MeOH (5 mL), and the filtrate was concentrated under reduced pressure. The crude material was purified via flash chromatography on silica gel (DCM/MeOH 95:5). Glycolipid **16a** was isolated as a white film (4 mg, 80% yield); [α]_D²⁵ -18 (c 0.08, DCM/MeOH 60:40); IR (neat) 3326, 2926, 2851, 1624, 1578 cm⁻¹; ¹H NMR (500 MHz, CDCl₃/MeOD 2:1 v/v) δ 7.01 (m, 4H), 6.83 (m, 3H), 6.64 (m, 2H), 6.52 (m, 1H), 4.59 (d *J* = 3.8 Hz, 1H), 3.97 (m, 2H), 3.89 (m, 1H), 3.84 (m, 2H), 3.78 (m, 1H), 3.55 (m, 1H), 3.49 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.42 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.35 (m, 2H), 3.27 (m, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.91 (t, *J* = 7.5 Hz, 2H), ¹³C NMR (125 MHz, CDCl₃/MeOD 2:1 v/v) δ 173.9, 143.4, 129.3 (d_{C-F}, *J* = 7.5 Hz), 128.9, 128.2, 127.4, 126.8, 114.4 (d_{C-F}, *J* = 20.9 Hz), 113.6, 99.2, 74.1, 71.7, 69.7, 69.1, 68.5, 63.9, 40.7, 36.1, 34.7, 33.3, 31.6, 31.3, 30.5, 29.3, 29.3, 29.1, 29.0, 28.8, 25.5, 25.3, 24.6, 22.3, 13.4; HRMS (ESI) for C₄₉H₇₉FNO₁₀ (M + H)⁺ *m/z*. calcd: 861.5770. Found: 861.6141.



(2*S*,3*S*,4*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-*O*-(6-*O*-hydrocinnamoyl- α -D-galactopyranosyl)octadecan-1,3,4-triol (16b**)**

(2*S*,3*S*,4*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl-6-hydrocinnamoyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-3,4-diol (**57b**) (8 mg, 0.007 mmol) was dissolved in EtOH/CHCl₃ (4:1 v/v, 0.6 mL) and purged with N₂ under stirring. Pd(OH)₂/C (50 mg) was added, and the reaction vessel was purged with H₂. The reaction mixture was stirred overnight under a H₂ balloon. It was then flushed with N₂ and filtered through celite. The celite pad was rinsed with DCM (5 mL) and MeOH (5 mL), and the filtrate was concentrated under reduced pressure. The crude material was purified via flash chromatography on silica gel (DCM/MeOH 95:5). Glycolipid **16b** was isolated as a white film (5 mg, 83% yield); [α]_D²⁰ −13 (c 0.1, DCM/MeOH 60:40); IR (neat) 3329 (br), 2925, 2852, 1625, 1509 cm^{−1}; ¹H NMR (500 MHz, CDCl₃/MeOD 2:1 v/v) δ 7.07 (m, 2H), 7.00 (m, 2H), 6.92 (m, 3H), 6.75 (m, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 4.71 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.05 (d, *J* = 5.6 Hz, 2H), 3.77 (m, 2H), 3.68 (m, 4H), 3.63 (m, 1H), 3.57 (m, 4H), 3.52 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.47 (m, 2H), 2.74 (t, *J* = 8.7 Hz, 2H), 2.47 (t, *J* = 8.0 Hz, 1H), 2.38 (m, 3H), 1.42 (m, 4H), 1.07 (m, 36H), 0.68 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃/MeOD 2:1 v/v) δ 174.5, 174.0, 161.5, 140.2, 129.5 (d_{C-F}, *J* = 7.8 Hz), 128.3, 128.1,

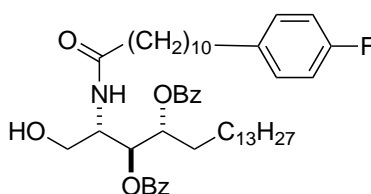
127.6, 126.1, 114.6 (d_{C-F} , $J = 20.9$ Hz), 113.8, 99.4, 74.4, 71.9, 70.5, 69.9, 68.6, 68.4, 60.5, 53.3, 37.1, 36.3, 35.5, 34.9, 33.5, 32.8, 32.3, 32.1, 31.7, 31.4, 30.6, 30.5, 29.9, 29.6, 29.5, 29.5, 29.3, 29.2, 29.0, 27.7, 27.2, 26.9, 26.3, 26.2, 26.0, 25.7, 25.3, 13.7; HRMS (ESI) for $C_{50}H_{81}FNO_{10}$ ($M + H$)⁺ m/z . calcd: 874.5844. Found: 874.5831.



Phenyl 2-O-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranosyl)-3,4,6-tri-O-benzyl-1-thio- β -D-galactopyranoside (17)

A solution of NaOMe in MeOH (0.50 M, 3.5 mL, 1.7 mmol) was added dropwise to a solution of phenyl-2-O-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranosyl)-3,4,6-tri-O-acetyl-1-thio- β -D-galactopyranoside (**25**) (0.51 g, 0.55 mmol) in MeOH (22 mL). After 2 h at rt, the reaction solution was neutralized with DOWEX resin. The mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to yield an orange oil. The oil was dissolved in DMF (17 mL). NaH (60% in mineral oil, 0.14 g, 3.4 mmol) was added, followed by benzyl bromide (0.32 g, 1.9 mmol), and the suspension was stirred at rt overnight. The excess NaH was quenched with MeOH (3 mL), and the reaction mixture was poured onto crushed ice. The mixture was extracted with Et₂O (3 x 50 mL), and the organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure. The crude material was purified via flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to yield a white solid (0.4 g, 67% over two steps).⁴³ ¹H NMR (400

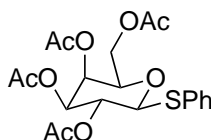
MHz, CDCl₃) δ 7.56 (m, 2H), 7.44–7.17 (m, 38H), 5.89 (d, J = 3.6 Hz, 1H), 4.95–4.86 (m, 4H), 4.82 (d, J = 2.7 Hz, 1H), 4.79 (d, J = 2.8 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.62–4.54 (m, 3H), 4.53 (d, J = 9.2 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 9.4 Hz, 1H), 4.33 (d, J = 12.0 Hz, 1H), 4.27 (d, J = 12.0 Hz, 1H), 4.15 (dd, J = 10.2, 3.7 Hz, 1H), 4.04 (d, J = 2.4 Hz, 1H), 3.91 (dd, J = 10.2, 2.7 Hz, 1H), 3.83 (m, 1H), 3.75 (dd, J = 9.4, 2.5 Hz, 1H), 3.71 (m, 3H), 3.50–3.41 (m, 2H).



(2S,3S,4R)-2-Amino-3,4-(di-O-benzoyl)-N-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (19**)**

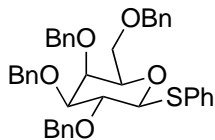
(2S,3S,4R)-2-Amino-3,4-(di-O-benzoyl)-N-(11-(4-fluorophenyl)undecanoyl)-1-(O-trityl)-octadecan-1,3,4-triol (**31**) (0.387 g, 0.376 mmol) was dissolved in DCM:MeOH (v/v 2:1, 11 mL). *p*-Toluenesulfonic acid monohydrate (0.036 g, 0.19 mmol) was added, and the reaction was stirred at rt for 7 h and was then diluted with EtOAc (20 mL). The mixture was then washed with 5% aqueous NaHCO₃ (20 mL) and brine (20 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified via flash chromatography on silica gel (petroleum ether/EtOAc 70:30) to yield **19** as a colorless oil (0.215 g, 73%): [α]_D²¹ +29.7 (c 1.2, DCM); IR (neat) 2922, 2852, 1719, 1509, 1450, 1263, 1095 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.04 (m, 2H), 7.94 (m, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (m, 3H), 7.37 (t, J = 7.8 Hz, 2H), 7.10 (m, 2H), 6.94 (m,

2H), 6.48 (d, $J = 9.3$ Hz, 1H), 5.45 (dd, $J = 9.6, 2.4$ Hz, 1H), 5.37 (m, 1H), 4.40 (dd, $J = 9.4, 9.4$ Hz, 1H), 3.65 (m, 2H), 2.93 (dd, $J = 8.4, 5.1$ Hz, 1H), 2.55 (t, $J = 7.5$ Hz, 2H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.03 (m, 2H), 1.69 (m, 2H), 1.57 (m, 2H), 1.25 (m, 36H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.5, 167.2, 166.6, 161.3 ($\text{d}_{\text{C-F}}$, $J = 241.3$ Hz), 138.7 ($\text{d}_{\text{C-F}}$, $J = 2.9$ Hz), 133.9, 133.3, 130.2, 129.9, 129.7, 129.4, 128.7 ($\text{d}_{\text{C-F}}$, $J = 7.3$ Hz), 115.1 ($\text{d}_{\text{C-F}}$, $J = 21.0$ Hz), 74.2, 73.8, 61.7, 50.2, 37.0, 35.3, 32.1, 31.8, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 28.6, 26.0, 25.9, 22.8, 14.3; HRMS (ESI) for $\text{C}_{49}\text{H}_{71}\text{FNO}_6$ ($\text{M} + \text{H}$) $^+$ m/z calcd: 788.5260. Found: 788.5240.



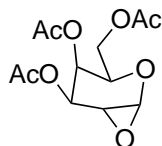
Phenyl-2,3,4,6-tetra-O-acetyl-1- β -D-thiogalactopyranoside (**22**)

Thiophenol (4.09 g, 37.1 mmol, 3.79 mL) was added to a solution of β -D-galactose pentacetate (5.00 g, 12.8 mmol) in dry DCM (50 mL) at 0 °C. After 30 min, BF_3 etherate (6.29 g, 44.3 mmol, 5.5 mL) was added dropwise, and the solution was left at rt for 3 days. The reaction mixture was diluted with DCM (50 mL), washed with saturated aqueous NaHCO_3 (75 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) afforded phenyl 2,3,4,6-tetra-O-acetyl-1- β -D-thiogalacto-pyranoside (**22**) as a white solid (3.68 g, 83%):⁴⁴ ^1H NMR (400 MHz, CDCl_3) δ 7.51–7.48 (m, 2H), 7.30–7.28 (m, 3H), 5.39 (d, $J = 3.2$ Hz, 1H), 5.22 (dd, $J = 10.0$ Hz, 1H), 5.04 (dd, $J = 9.9, 3.3$ Hz, 1H), 4.71 (d, $J = 10.0$ Hz, 1H), 4.16 (dd, $J = 11.4, 7.1$ Hz, 1H), 4.10 (dd, $J = 11.3, 6.1$ Hz, 1H), 3.93 (dd, $J = 6.4, 6.4$ Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H).



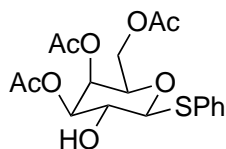
Phenyl-2,3,4,6-tetra-O-benzyl-1-β-D-thiogalactopyranoside (**23**)

NaOMe in MeOH (4.37 M, 24.6 mmol, 5.62 mL) was added to a solution of phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside (**22**) (2.70 g, 6.14 mmol) in THF (40 mL), and the solution was left at rt for 4 h. The reaction mixture was neutralized using Dowex (C-211, H, 16-50 mesh) resin. The resin was filtered, and the filtrate was concentrated to afford phenyl 1-thio-β-D-galactopyranoside as a pale brown solid (1.64 g). The crude product was then dissolved in DMF (35 mL), and benzyl bromide (4.84 g, 28.3 mmol, 3.37 mL) was added, followed by NaH (60% in mineral oil, 1.97 g, 49.4 mmol) at 0 °C. The resulting suspension was stirred at rt overnight. The reaction mixture was diluted with H₂O (100 mL) at 0 °C and then extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to afford phenyl 2,3,4,6-tetra-O-benzyl-1-β-D-thiogalactopyranoside as a white solid (2.74 g, 72%):⁴⁴ ¹H NMR (400 MHz, CDCl₃) δ 7.62–7.60 (m, 2H), 7.43–7.29 (m, 20H), 7.23–7.22 (m, 3H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.78 (d, *J* = 9.7 Hz, 1H), 4.77–4.74 (m, 2H), 4.69 (d, *J* = 9.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.02 (d, *J* = 1.9 Hz, 1H), 3.98 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.71–3.64 (m, 4H).



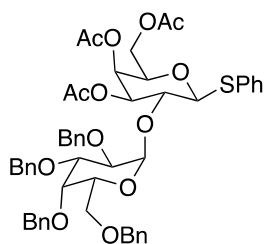
Tri-O-acetylgalactalepoxyde

Saturated NaHCO_3 (150 mL) and acetone (10 mL) were added to a solution of 3,4,6-tri-O-acetylgalactal (5.74 g, 21.1 mmol) in DCM (100 mL). After stirring for 10 min, Oxone (26.0 g, 42.2 mmol) was added slowly at 0 °C. The mixture was stirred at 0 °C for 30 min and at rt for 5 h. The reaction mixture was diluted with DCM (20 mL), and the layers were separated. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give tri-O-acetylgalactalepoxyde as a viscous oil (5.39 g). The product was azeotroped with toluene (2 x 40 mL) and used in the next reaction without further purification:⁴⁵ ^1H NMR (300 MHz, CDCl_3) δ 5.25 (d, J = 4.0 Hz, 1H), 5.19 (d, J = 4.1 Hz, 1H), 5.08 (d, J = 2.1 Hz, 1H), 4.16–4.10 (m, 2H), 4.05 (dd, J = 13.0, 6.6 Hz, 1H), 3.02 (m, 1H), 2.15 (s, 3H), 2.09 (s, 6H).



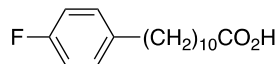
Phenyl 3,4,6-tri-O-acetyl-1-β-D-thiogalactopyranoside (24)

Thiophenol (8.24 g, 74.8 mmol) and triethylamine (15.2 g, 150 mmol, 21.0 mL) were added to a solution of tri-O-acetylgalactalepoxide (5.39 g, 18.7 mmol) in THF (60 mL). After stirring for 24 h, the resulting solution was concentrated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10 to 70:30) to give phenyl 3,4,6-tri-O-acetyl-1-β-D-thiogalacto-pyranoside (**24**) as a pale yellow oil (2.76 g, 63% over 2 steps):⁴⁵ ¹H NMR (400 MHz, CDCl₃) δ 7.62–.59 (m, 2H), 7.37–7.35 (m, 3H), 5.43 (d, *J* = 3.1 Hz, 1H), 4.98 (dd, *J* = 9.7, 3.2 Hz, 1H), 4.64 (d, *J* = 9.7 Hz, 1H), 4.21 (dd, *J* = 11.3, 6.9 Hz, 1H), 4.14 (dd, *J* = 10.9, 6.2 Hz, 1H), 3.97 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.84 (ddd, *J* = 12.3, 9.7, 2.6 Hz, 1H), 2.44 (d, *J* = 2.6 Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H).



Phenyl-2-O-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranosyl)-3,4,6-tri-O-acetyl-1-thio- β -D-galactopyranoside (25**)**

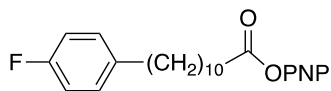
Phenyl 2,3,4,6-tetra- O-benzyl-1- β -D-thiogalactopyranoside (**23**) (1.80 g, 2.85 mmol) and phenyl 3,4,6-tri- O-acetyl-1- β -D-thiogalactopyranoside (**24**) (1.25 g, 3.14 mmol) were dried by azeotroping with toluene (3 x 40 mL). The mixture was dissolved in DCM (60 mL) under N₂, and freshly ground activated 4 Å MS (2.0 g) were added. The mixture was cooled to –45 °C, and *N*-iodosuccinimide (0.802 g, 3.56 mmol) and silver triflate (0.217 g, 0.840 mmol) were added. The mixture was stirred at –45 °C until the donor was consumed (based on TLC and a color change to magenta). Et₃N (20 mL) was added. The reaction mixture was diluted with DCM (100 mL) and filtered through a pad of celite. The celite was washed with DCM (50 mL). The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10 to 60:40) to afford phenyl 2-O-(2,3,4,6-tetra- O-benzyl- β -D-galactopyranosyl)-3,4,6-tri- O-acetyl-1-thio- α -D-galactopyranoside (**25**) as a viscous oil (1.58 g, 60%).⁴³ ¹H NMR (400 MHz, CDCl₃) δ 7.54–7.52 (m, 2H), 7.41–7.26 (m, 23H), 5.71 (d, *J* = 3.6 Hz, 1H), 5.46 (d, *J* = 2.9 Hz, 1H), 5.10 (dd, *J* = 9.5, 3.2 Hz, 1H), 5.01–4.75 (m, 6H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.49–4.40 (m, 2H), 4.22–3.91 (m, 8H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.50 (dd, *J* = 8.5, 5.1 Hz, 1H), 2.06 (s, 6H), 1.97 (s, 3H).



11-(4-Fluorophenyl)undecanoic acid (26)

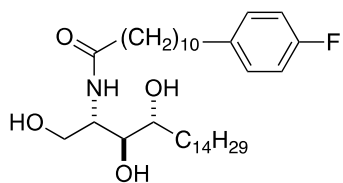
4-Fluoroiodobenzene (2.77 g, 12.5 mmol) and 10-undecynoic acid (3.11 g, 17.1 mmol) were dissolved in Et₃N (28 mL). Bis(triphenyl phosphine) palladium (II) dichloride (0.700 g, 0.998 mmol) was then added to the reaction flask. The mixture was stirred for 5 min, and copper (I) iodide (1.28 g, 6.74 mmol) was added. The reaction mixture was heated to 50 °C and stirred under N₂ overnight. The mixture was allowed to cool to rt and passed through a pad of celite. The celite was rinsed with Et₂O (500 mL). The filtrate was concentrated. The resulting crude material was a brown solid:⁴⁷ ¹H NMR (400 MHz, CDCl₃) δ 7.35 (m, 2H), 6.97 (m, 2H), 2.34 (m, 2H), 1.56 (m, 3H), 1.27 (m, 10H);

The crude 11-(4-fluorophenyl)undec-10-ynoic acid was dissolved in MeOH (120 mL) under N₂. Pd/C (3.00 g) and AcOH (6 mL) were added. The reaction vessel was purged with H₂ for 10 min. The reaction was then stirred overnight at rt under a H₂ balloon. The suspension was filtered through celite, and the celite was washed with CHCl₃/MeOH (v/v 1:1, 150 mL) and concentrated under reduced pressure. The crude product was purified via flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to yield a white solid (2.81 g, 80% over 2 steps):⁴⁷ ¹H NMR (400 MHz, CDCl₃) δ 7.10 (m, 2H), 6.97 (m, 2H), 3.67 (s, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.59 (m, 4H), 1.30 (m, 12H).



4-Nitrophenyl-11-(4-fluorophenyl)undecanoate (**27**)

11-(4-Fluorophenyl)undecanoic acid (**26**) (0.672 g, 2.40 mmol), 4-nitrophenol (0.303 g, 2.18 mmol), and DMAP (0.0530 g, 0.436 mmol) were dissolved in dry DCM (100 mL), and the solution was stirred for 15 min at rt. DCC (0.468 g, 2.27 mmol) was dissolved in dry DCM (20 mL) then added to the reaction flask. The reaction mixture was stirred overnight and was then concentrated under reduced pressure. The crude material was purified via flash chromatography on silica gel (petroleum ether/EtOAc 95:5) to give **27** as a white solid (0.89 g, 90%): mp 37.7–38.5 °C; IR (neat) 2922, 2851, 1758, 1527, 1343, 1200, 1141 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.25 (m, 2H), 7.28 (m, 2H), 7.12 (m, 2H), 6.95 (m, 2H), 2.60 (t, $J = 7.44$ Hz, 2H) 2.58 (t, $J = 7.56$ Hz, 2H), 1.76 (quint, $J = 7.36$ Hz, 2H), 1.58 (m, 2H), 1.31 (m, 12H); ^{13}C NMR (100 MHz CDCl_3) δ 171.1, 161.0 ($d_{\text{C-F}} J = 241.5$ Hz), 155.4, 145.0, 138.3 ($d_{\text{C-F}} J = 3.1$ Hz), 129.5 ($d_{\text{C-F}} J = 7.8$ Hz), 124.9, 122.3, 114.7 ($d_{\text{C-F}} J = 21.1$ Hz), 35.1, 34.3, 31.6, 29.6, 29.5, 29.5, 29.3, 29.2, 29.1, 24.7; HRMS (ESI) for $\text{C}_{23}\text{H}_{28}\text{FNNaO}_6$ ($\text{M} + \text{Na}$) $^+$ m/z calcd: 424.1885. Found: 424.1868.

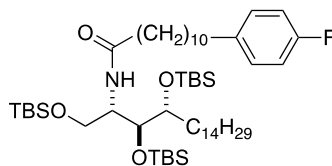


(2S,3S,4R)-2-Amino-N-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol

(28)

4-Nitrophenyl-11-(4-fluorophenyl)undecanoate **27** (0.361 g, 0.900 mmol) and phytosphingosine (**20**) (0.238 g, 0.750 mmol) were combined in THF (18 mL) and stirred at rt. Et₃N (0.36 mL) was added, and the reaction was stirred for 2 d at 50 °C. The solution was concentrated under reduced pressure, and the resulting solid was purified via flash chromatography on silica gel (petroleum ether/EtOAc/MeOH 50:47:3) to give **27** as a white solid (0.435 g, 92%): mp 109.5–111.2 °C; [α]_D²¹ –116 (c 0.6, MeOH); IR (neat) 3371 (br), 3327 (br), 2917, 2849, 1611, 1556, 1510, 1467, 1261, 1233, 1095 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.11 (m, 2H), 6.94 (m, 2H), 6.32 (d, *J* = 7.4 Hz, 1H), 4.13 (m, 1H), 3.91 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.87 (d, *J* = 7.0 Hz, 1H), 3.73 (dd, *J* = 11.2, 5.3 Hz, 2H), 3.58 (m, 3H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.56 (br, 1H) 2.23 (t, *J* = 7.4 Hz, 2H), 1.77 (m, 1H), 1.57 (m, 8H), 1.25 (m, 36H), 0.88 (t, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz CDCl₃/MeOD v/v 2:1) δ 174.6, 161.1 (d_{C-F} *J* = 241.0 Hz), 138.4, 129.5 (d_{C-F} *J* = 7.5 Hz), 114.7 (d_{C-F} *J* = 20.9 Hz), 75.5, 72.4, 61.0, 51.9, 36.4, 35.0, 32.9, 31.8, 31.5, 29.6, 29.5, 29.4, 29.3, 29.1,

25.8, 25.7, 22.6, 13.9; HRMS (ESI) for C₃₅H₆₃FNO₄ (M + H)⁺ *m/z* calcd: 580.4741. Found: 580.4717.

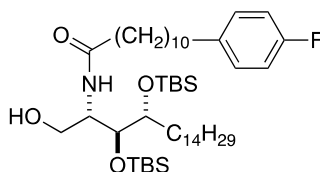


(2*S*,3*S*,4*R*)-2-Amino-1,3,4-(tri-*O*-*tert*-butyldimethylsilyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (29**)**

(2*S*,3*S*,4*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (**28**)

(0.206 g, 0.355 mmol) was suspended in DCM (2.5 mL) at 0 °C. TBDMSOTf (0.845 g, 3.20 mmol) dissolved in 2,6-lutidine (0.82 mL) was added, and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with H₂O (8 mL) and extracted with DCM (2 x 16 mL). The organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure. The crude product was purified via flash chromatography on silica gel (petroleum ether/EtOAc 95:5) to give **29** as a colorless oil (0.226 g, 69%): [α]_D²² −0.69 (*c* 0.12, DCM); IR (neat) 2926, 2854, 833, 775 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.11 (m, 2H), 6.94 (m, 2H), 5.81 (d, *J* = 8.5 Hz, 1H), 3.95 (m, 1H), 3.86 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.82 (dd, *J* = 7.3, 1.0 Hz, 1H), 3.68 (m, 1H), 3.63 (dd, *J* = 10.1, 4.5 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.14 (t, *J* = 7.6 Hz, 2H), 1.58 (m, 6H), 1.27 (m, 36H), 0.90 (m, 30H), 0.13 (s, 3H), 0.06 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 161.3 (*d*_{C-F}, *J* = 244.5 Hz), 138.6 (*d*_{C-F}, *J* = 2.9 Hz), 129.8 (*d*_{C-F}, *J* = 7.7 Hz), 115.1 (*d*_{C-F}, *J* = 21.2 Hz), 75.7, 75.6, 61.6, 52.8, 37.3, 35.3, 32.4, 32.1, 31.8, 30.2,

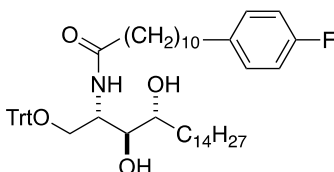
29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.4, 26.5, 26.3, 26.3, 26.2, 26.1, 26.0, 25.9, 25.8, 25.7, 25.7, 22.9, 18.5, 18.4, 18.3, 18.3, 14.3, 1.4, 1.2, -2.8, -2.8, -3.3, -3.6, -3.9, -4.6, -4.9, -5.0, -5.4; HRMS (ESI) for C₅₃H₁₀₅FNO₄Si₃ (M + H)⁺ *m/z* calcd: 922.7335. Found: 922.7358.



(2*S*,3*S*,4*R*)-2-Amino-3,4-(di-*O*-*tert*-butyldimethylsilyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (30**)**

(2*S*,3*S*,4*R*)-2-Amino-1,3,4-(tri-*O*-*tert*-butyldimethylsilyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (**29**) (0.165 g, 0.180 mmol) was dissolved in THF (2 mL) at 0 °C. A mixture of H₂O/TFA (10:1/0.83 mL) was also cooled to 0 °C and added to the solution. The reaction was monitored by TLC until the starting material was consumed. The mixture was neutralized with saturated aqueous NaHCO₃ (2 mL) and extracted with DCM (2 x 10 mL). The organic layers were combined and dried (MgSO₄). The solution was concentrated under reduced pressure, and the crude product was purified via flash column chromatography on silica gel (petroleum ether/EtOAc 85:15) to yield **30** as a clear, colorless oil (0.125 g, 86%): [α]_D²⁵ −8.2 (*c* 1.5, DCM); IR (neat) 2924, 2853, 1509, 1250, 832, 774 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) δ 7.11 (m, 2H), 6.94 (m, 2H), 6.24 (d, *J* = 7.8 Hz, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 4.06 (m, 1H), 3.91 (t, *J* = 2.8 Hz, 1H), 3.76 (ddd, *J* = 6.4, 2.5 Hz, 1H), 3.58 (m, 1H), 3.15 (d, *J* = 6.4 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.18 (t, *J* = 7.6 Hz, 2H), 1.58 (m, 6H), 1.26 (m, 36 H), 0.93 (s, 9H), 0.91 (s, 9H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.11 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 161.3

(d_{C-F} , $J = 242.6$ Hz) , 138.9 (d_{C-F} , $J = 2.9$ Hz), 130.1 (d_{C-F} , $J = 7.91$ Hz), 115.3 (d_{C-F} , $J = 20.9$ Hz), 77.9, 77.8, 64.1, 51.8, 37.4, 35.6, 34.9, 32.4, 32.1, 30.3, 30.2, 30.1, 30.0, 30.0, 29.9, 29.8, 29.7, 26.5, 26.5, 26.3, 26.1, 23.2, 18.6, 18.6, 14.6, -3.3, -3.6, -4.0, -4.4; HRMS (ESI) for $C_{47}H_{91}FNO_4Si_2$ ($M + H$)⁺ m/z calcd: 808.7335. Found: 808.6487.

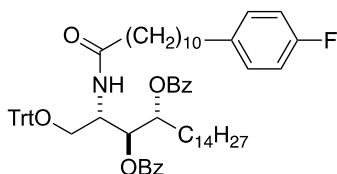


(2S,3S,4R)-2-Amino-N-(11-(4-fluorophenyl)undecanoyl)-1-(O-trityl)octadecan-1,3,4-triol

(2S,3S,4R)-2-Amino-N-(11-(4-fluorophenyl)undecanoyl)-octadecan-1,3,4-triol (28)

(0.280 g, 0.484 mmol) was dissolved in EtOAc (3.2 mL) and Et₃N (0.66 mL). TrtCl (0.270 g, 0.969 mmol) was added, and the reaction solution was stirred at 75 °C for 4 h. The reaction mixture was concentrated under reduced pressure and purified via flash chromatography on silica gel (petroleum ether/EtOAc/Et₃N 70:25:5) to give (2S,3R,4R)-2-amino-N-(11-(4-fluorophenyl)undecanoyl)-1-(O-trityl)octadecan-1,3,4-triol as a clear, yellow oil (0.365 g, 92%): $[\alpha]_D^{25} +4.4$ (c 1.0, DCM); IR (neat) 2922, 2852, 1638, 1509, 1448, 1220 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 7.42 (m, 6H), 7.32 (m, 6H), 7.25 (m, 3H), 7.10 (m, 2H), 6.95 (m, 2H), 6.00 (d, $J = 8.3$ Hz, 1H), 4.26 (m, 1H), 3.57 (m, 1H), 3.50 (dd, $J = 9.8, 3.6$ Hz, 1H), 3.39 (m, 1H), 3.35 (dd, $J = 9.9, 4.7$ Hz, 1H), 3.07 (d, $J = 8.4$, 1H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.15 (t, $J = 7.5$ Hz, 2H), 1.56 (m, 6H), 1.45 (m, 3H), 1.24 (m, 34H), 0.88 (t, $J = 6.6$ Hz, 3H); ¹³C NMR (100 MHz CDCl₃) δ 173.2, 161.8 (d_{C-F} , $J = 244.8$ Hz), 143.2, 138.5 (d_{C-F} , $J = 3.0$ Hz), 133.1, 129.7 (d_{C-F} , $J = 7.8$ Hz), 128.5, 128.1, 127.6, 127.4,

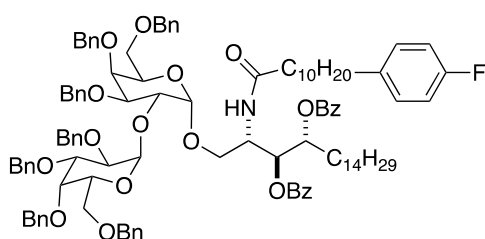
115.4, 115.2, 114.9 (d_{C-F}, $J = 21.0$ Hz), 87.6, 75.7, 72.9, 62.9, 60.5, 50.1, 36.5, 35.2, 33.3, 32.0, 31.8, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 26.0, 25.8, 22.8, 21.2, 14.3; HRMS (ESI) for C₅₄H₇₇FNNaO₆ (M + Na)⁺ m/z calcd: 844.5651. Found: 844.5672.



(2*S*,3*S*,4*R*)-2-Amino-3,4-(di-*O*-benzoyl)-*N*-(11-(4-fluorophenyl)undecanoyl)-1-(*O*-trityl)octadecane-1,3,4-triol (31**)**

(2*S*,3*S*,4*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-(*O*-trityl)octadecan-1,3,4-triol (0.532 g, 0.647 mmol) was dissolved in pyridine (9.0 mL). DMAP (9.58 mg, 0.0784 mmol) was added to the solution; then BzCl (0.656 g, 0.54 mL, 4.67 mmol) was added drop wise and the reaction stirred overnight. The reaction was quenched with H₂O (15 mL), and then the solution was extracted with CHCl₃ (2 x 15mL). The combined organic extracts were combined, dried (MgSO₄), and concentrated under reduced pressure. The crude material was purified via flash chromatography on silica gel (petroleum ether/EtOAc/Et₃N 90:5:5 then increased to petroleum ether/EtOAc 93:7) to give **31** as a clear, colorless oil (0.526 g, 79%): $[\alpha]_D^{25} -4.1$ (c 0.15, DCM); IR (neat) 2925, 2853, 1723, 1509, 1449, 1275, 1095, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.95 (m, 2H), 7.88 (m, 2H), 7.56 (m, 2H), 7.40, (m, 4H), 7.29 (m, 6H), 7.12 (m, 11H), 6.95 (m, 2H), 5.97 (d, $J = 9.3$ Hz, 1H), 5.78 (dd, $J = 9.0, 2.6$ Hz, 1H), 5.34 (ddd, $J = 9.7, 2.8, 2.8$ Hz, 1H), 4.58 (m, 1H), 3.33 (dd, $J = 9.9, 3.8$ Hz, 1H), 3.28 (dd, $J = 9.7, 3.0$ Hz, 1H), 2.56 (t, $J = 7.5$ Hz, 2H), 2.16 (m, 2H), 1.85 (m, 2H), 1.59 (m, 5H), 1.24 (m, 35H), 0.88 (m, 3H); ¹³C NMR (100 MHz CDCl₃) δ 173.0, 166.7,

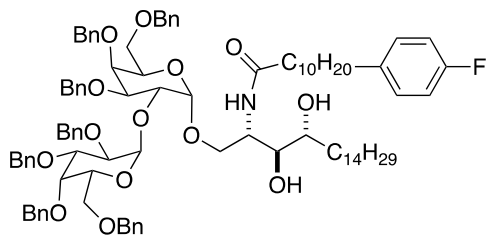
165.2, 161.4 (d_{C-F} , $J = 241.4$ Hz), 143.5, 138.7 (d_{C-F} $J = 3.0$ Hz), 133.3, 133.1, 130.4, 130.0, 130.0, 129.9 (d_{C-F} , $J = 7.6$ Hz), 129.8, 129.8, 128.8, 128.7, 128.6, 128.5, 127.3, 127.2, 127.1, 115.2, 115.0 (d_{C-F} $J = 21.0$ Hz), 87.1, 74.4, 73.9, 73.0, 72.8, 61.9, 53.6, 49.6, 48.9, 37.1, 35.4, 34.7, 32.1, 31.9, 30.2, 29.9, 29.8, 29.8, 29.7, 29.7, 29.6, 29.4, 29.4, 28.7, 28.3, 25.9, 25.9, 25.1, 22.9, 14.3; HRMS (ESI) for $C_{68}H_{85}FNO_6$ ($M + H$)⁺ m/z calcd: 1030.6361. Found: 1030.6390.



(2*S*,3*S*,4*R*)-2-Amino-3,4-(di-*O*-benzoyl)-1-*O*-[2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-*D*-galactopyranosyl]-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (32)

Phenyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-3,4,6-tri-*O*-benzyl-1-thio-β-*D*-galactopyranoside (**17**) (0.122 g, 0.116 mmol) and (2*S*,3*S*,4*R*)-2-amino-3,4-(di-*O*-benzoyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol **31** (0.126 g, 0.162 mmol) were azeotroped with toluene. Silver triflate (0.010 g, 0.037 mmol) was separately azeotroped with toluene. The donor and acceptor were dissolved in DCM (7.7 mL) at -40 °C under N₂. Silver triflate and NIS (0.033 g, 0.145 mmol) were added, and the reaction mixture was stirred at -20 °C for 2.5 hr. The reaction was quenched with Et₃N (1 mL). The crude mixture was filtered through celite and concentrated under reduced pressure.

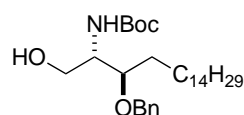
The crude mixture was purified via flash column chromatography on silica gel (petroleum ether/EtOAc 90:10), which gave **32** as a clear, yellow oil (0.103 g, 60%): $[\alpha]^{25}_{\text{D}} -25.9$ (c 0.80, DCM); IR (neat) 2924, 2853, 1720, 1508, 1453, 1274, 1095, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J = 7.7$ Hz, 2H), 7.84 (d, $J = 7.7$ Hz, 2H), 7.44 (m, 2H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.27–7.10 (m, 37H), 7.02 (m, 2H), 6.86 (m, 2H), 6.75 (d, $J = 9.2$ Hz, 1H), 5.52 (d, $J = 9.1$ Hz, 1H), 5.33 (m, 1H), 4.89 (d, $J = 2.9$ Hz, 1H), 4.81 (d, $J = 2.7$ Hz, 1H), 4.74 (t, $J = 10.6$ Hz, 2H), 4.62 (m, 2H), 4.57–4.35 (m, 9H), 4.21 (m, 2H), 4.12 (m, 2H), 3.90 (m, 2H), 3.72 (m, 3H), 3.49 (m, 2H), 3.42 (m, 2H), 3.26 (m, 2H), 2.47 (t, $J = 7.6$ Hz, 2H), 2.07 (m, 2H), 1.83 (m, 2H), 1.50 (m, 4H), 1.17 (m, 36H), 0.79 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.6, 166.2, 165.5, 161.3 ($d_{\text{C-F}}$, $J = 243.9$ Hz), 139.2, 138.9, 138.9, 138.8, 138.6, 138.5, 138.4, 138.0, 137.9, 133.3, 132.9, 130.4, 130.2, 129.9, 129.8 ($d_{\text{C-F}}$, $J = 7.7$ Hz), 129.7, 129.2, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 115.0 ($d_{\text{C-F}}$, $J = 21.0$ Hz), 99.8, 96.5, 79.2, 76.5, 75.9, 74.9, 74.8, 74.7, 74.6, 73.9, 73.6, 73.4, 73.3, 73.2, 73.1, 72.9, 72.7, 72.3, 71.7, 70.6, 69.4, 69.2, 68.8, 68.5, 68.1, 67.2, 48.9, 48.4, 36.8, 36.6, 35.3, 32.1, 31.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 28.7, 25.9, 25.8, 22.8, 14.3; HRMS (ESI) for $\text{C}_{110}\text{H}_{133}\text{FNO}_{16}$ ($\text{M} + \text{H}$) $^+$ m/z calcd: 1742.9608. Found: 1742.9610.



(2*S*,3*S*,4*R*)-2-Amino-1-O-[2-O-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranosyl)-3,4,6-tri-O-benzyl- α -D-galactopyranosyl]-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol

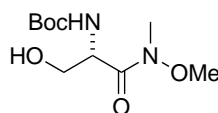
(2*S*,3*R*,4*R*)-2-Amino-3,4-(di-O-benzoyl)-1-O-[2-O-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranosyl)-3,4,6-tri-O-benzyl- α -D-galactopyranosyl]-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (**32**) (0.100 g, 0.067 mmol) was dissolved in MeOH/THF (v/v 1:1, 6.5 mL). NaOMe (0.5 M, 0.39 mmol, 0.78 mL) was added, and the reaction was stirred under N₂ for 2.5 hr. The reaction was neutralized with DOWEX resin, filtered through celite and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (petroleum ether/EtOAc 70:30) to give (2*S*,3*S*,4*R*)-2-amino-1-O-[2-O-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranosyl)-3,4,6-tri-O-benzyl- α -D-galactopyranosyl]-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol as a colorless oil (0.038 g, 88%): ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.24 (m, 31H), 7.13 (m, 3H), 6.95 (m, 2H), 6.41 (d, *J* = 8.3 Hz, 1H), 5.01 (d, *J* = 3.4 Hz, 1H), 4.85–4.74 (m, 5H), 4.68–4.49 (m, 6H), 4.39 (m, 1H), 4.28 (m, 1H), 4.23–4.19 (m, 3H), 4.14–4.08 (m, 3H), 4.01 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.94 (m, 2H), 3.87–3.83 (m, 3H), 3.57 (m, 1H), 3.51–3.47 (m, 4H), 3.31 (dd, *J* = 8.8, 5.1 Hz, 1H), 2.55 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 1H), 2.14 (t, *J* = 7.3 Hz, 2H), 1.58 (m, 6H), 1.26 (m, 38H), 0.89 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (125

MHz, CDCl₃) δ 173.3, 161.3 (d_{C-F}, J = 240.8 Hz), 138.9, 138.8, 138.7, 138.6 (d_{C-F}, J = 3.0 Hz), 138.5, 138.3, 138.0, 137.8, 129.8 (d_{C-F}, J = 7.6 Hz), 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 127.8, 127.7, 127.7, 127.6, 127.4, 115.0 (d_{C-F}, J = 21.0 Hz), 98.9, 98.0, 79.4, 77.9, 76.4, 75.7, 75.1, 75.0, 74.9, 74.8, 74.4, 74.3, 73.8, 73.4, 73.4, 72.6, 72.4, 70.1, 70.0, 69.3, 69.1, 68.3, 49.5, 36.8, 35.3, 34.0, 32.7, 32.1, 31.8, 29.9, 29.8, 29.7, 29.6, 29.4, 29.4, 29.3, 29.3, 26.6, 25.9, 24.9, 22.9, 14.3; HRMS (ESI) for C₉₆H₁₂₅FNO₁₄ (M + H)⁺ m/z calcd: 1534.9084. Found: 1534.9054.



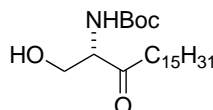
(2*S*,3*R*)-2-(*N*-*tert*-Butoxycarbonyl)amino-3-benzyloxyoctadecan-1-ol (34)

TBAF (1.0 M in THF, 3.3 mL, 3.3 mmol) was added to a solution of (2*S*,3*R*)-2-(*N*-*tert*-butoxycarbonyl)amino-1-*tert*-butyldiphenylsilyloxy-3-benzyloxyoctadecane (**39**) (1.20 g, 1.64 mmol) in THF (7.8 mL) under N₂ at 0 °C. The cooling bath was removed, and the mixture was stirred for 4 h at rt. The reaction mixture was concentrated, and the residue was dissolved in CHCl₃ (20 mL), washed with brine (10 mL), dried (MgSO₄) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5 to 85:15) afforded **33** as a white solid (0.735 g, 91%):²⁸ ¹H NMR (400 MHz, CDCl₃) δ 7.32 (m, 5H), 5.27 (d, J = 7.4 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 11.4 Hz, 1H), 3.95 (m, 1H), 3.65 (m, 3H), 2.95 (s, 1H), 1.67 (m, 1H), 1.44 (s, 9H), 1.26 (br s, 27H), 0.88 (t, J = 6.8 Hz, 3H).



[2-Hydroxy-1-(methoxymethylcarbonyl)ethyl]-carbamic acid *tert*-Butyl Ester (37)

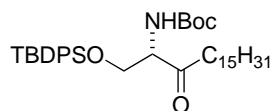
Boc-L-serine (8.00 g, 39.0 mmol) was dissolved in dry DCM (153 mL) and the solution cooled to $-15\text{ }^{\circ}\text{C}$ under N_2 . *N,O*-Dimethylhydroxylamine hydrochloride (3.92 g, 40.0 mmol) was added, followed by *N*-methylmorpholine (4.42 mL, 40.2 mmol). After 5 min 1-(3-methylaminopropyl-3-ethylcarbodiimide hydrochloride (7.70 g, 40.2 mmol) was added in five portions over 30 min. After being stirred for 1 h at $-15\text{ }^{\circ}\text{C}$, the reaction was quenched with HCl (1 M, 25 mL), and the layers were separated. The aqueous layer was extracted with DCM (3 \times 50 mL). The organic extracts were combined, washed with saturated aqueous NaHCO_3 (23 mL) and H_2O (23 mL), dried (MgSO_4), and concentrated to provide **37** as a white solid (8.52 g, 88%):²⁸ ^1H NMR (400 MHz, CDCl_3) δ 5.71 (br s, 1H), 4.95 (br s, 1H), 3.82–3.78 (m, 5H), 3.23 (s, 3H), 2.90 (br s, 1H), 1.43 (s, 9H).



(2S)-2-(*N-tert*-Butoxycarbonylamino)-1-hydroxyoctadecan-3-one (38)

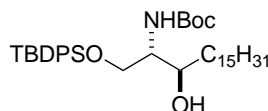
s-BuMgCl (2.0 M in THF, 19.5 mL, 38.9 mmol) was added dropwise to a solution of (2S)-methyl-[2-hydroxyl-(methoxymethylcarbonyl)ethyl]carbamic acid *tert*-butyl ester **37** (4.60 g, 18.5 mmol) in THF (60 mL) at $-15\text{ }^{\circ}\text{C}$. After stirring for 5 min, pentadecylmagnesium bromide (0.6 M in THF, 36.5 mL, 22.2 mmol) was added at $-15\text{ }^{\circ}\text{C}$; the resulting solution was warmed to rt and stirred overnight. The reaction mixture

was cooled to $-15\text{ }^{\circ}\text{C}$. Aqueous HCl (1M, 40 mL) was added, followed by EtOAc (40 mL), and the two layers were separated. The aqueous layer was extracted with DCM (3 x 50 mL), and the combined organic extracts were washed with H_2O (50 mL), dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel yielded **36** as a white solid (5.54 g, 74%):²⁸ ^1H NMR (400 MHz, CDCl_3) δ 5.48 (br s, 1H), 4.26 (m, 1H), 3.94 (m, 2H), 2.63 (br s, 1H), 2.55 (m, 2H), 1.57 (m, 2H), 1.45 (s, 9H), 1.20 (s, 24H), 0.80 (t, $J = 6.8\text{ Hz}$, 3H).



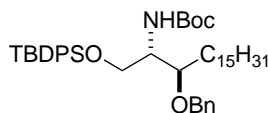
(2S)-2-(*N*-*tert*-Butoxycarbonylamino)-1-(*tert*-butyldiphenylsilyloxy)octadecan-3-one (39)

4-DMAP (0.264 g, 2.16 mmol), imidazole (2.20 g, 32.4 mmol) and TBPSCI (3.55 g, 12.9 mmol, 3.40 mL) were added to a solution of (2S)-2-(*N*-*tert*-butoxycarbonylamino)-1-hydroxyoctadecan-3-one (**36**) (4.30 g, 10.8 mmol) in DMF (30 mL). After stirring at rt overnight, the reaction mixture was diluted with Et_2O (150 mL). The resulting solution was then washed with H_2O (3 x 50 mL), dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) yielded **37** as a colorless oil (6.55 g, 95%):²⁸ ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.60 (m, 10H), 5.53 (d, $J = 1.1\text{ Hz}$, 1H), 4.33 (d, $J = 1.9\text{ Hz}$, 1H), 4.04 (dd, $J = 10.6, 3.1\text{ Hz}$, 1H), 3.90 (dd, $J = 10.9, 3.8\text{ Hz}$, 1H), 2.51 (m, 2H), 1.58 (m, 2H), 1.44 (s, 9H), 1.26 (m, 24H), 1.03 (s, 9H), 0.89 (t, $J = 7.0\text{ Hz}$, 3H).



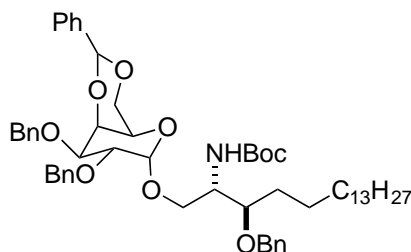
(2*S*,3*R*)-2-(*N*-*tert*-Butoxycarbonylamino)-1-(*tert*-butyldiphenylsilyloxy)octadecan-3-ol (40)

LiAl(Ot-Bu)₃H (8.03 g, 31.6 mmol) was added to dry EtOH (40 mL) at –78 °C. After stirring for 20 min, a solution of (2*S*)-2-*N*-*tert*-butoxycarbonylamino)-1-(*tert*-butyldiphenylsilyloxy)octadecan-3-one (**37**) (3.36 g, 5.26 mmol) in dry EtOH (40 mL) was added slowly, and stirring at –78 °C was continued for 6 h. The reaction mixture was diluted with aqueous citric acid (10%, 100 mL) and allowed to warm to rt over 1.5 h, and the resulting suspension was extracted with DCM (3 x 100 mL). The combined organic extracts were washed with H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography on silica gel (petroleum ether/EtOAc, 95:5 to 90:10) to yield **38** as a colorless oil (3.27 g, 97%).²⁸ ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.65 (m, 10H), 5.30 (d, *J* = 8.1 Hz, 1H), 3.93 (m, 1H), 3.90 (d, *J* = 10.4 Hz, 1H), 3.67 (m, 1H), 3.57 (s, 1H), 2.88 (d, *J* = 8.1 Hz, 2H), 1.57 (m, 2H), 1.45 (s, 9H), 1.27 (m, 25H), 1.1 (s, 9H), 0.87 (t, *J* = 6.6 Hz, 3H).



(2*S*,3*R*)-3-(Benzyloxy)-2-(*N*-*tert*-butoxycarbonylamino)-1-(*tert*-butylphenylsilyloxy)octadecane (41)

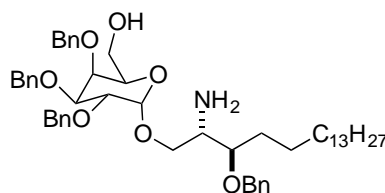
Tetrabutylammonium iodide (1.40 g, 4.33 mmol) and benzyl bromide (0.809 g, 4.73 mmol, 0.56 mL) were added to a solution of (2*S*,3*R*)-2-(*N*-*tert*-butoxycarbonyl-amino)-1-(*tert*-butyldiphenylsilyloxy)octadecan-3-ol (**38**) (2.52 g, 3.94 mmol) in DMF (20 mL) at 0 °C. After stirring for 10 min, NaH (60% in mineral oil, 0.189 g, 4.73 mmol) was added at 0 °C, and stirring at 0 °C was continued for 20 min. The mixture was allowed to warm to at rt and stirred overnight. The resulting solution was diluted with saturated aqueous NH₄Cl (100 mL) and extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with H₂O (2 x 100 mL) and brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 100:0 to 95:5) provided **39** as a pale yellow oil (2.24 g, 78%):²⁸ ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.65 (m, 15H), 4.71 (d, *J* = 8.0 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.49 (dd, *J* = 10.0, 4.9 Hz, 2H), 3.86 (dd, *J* = 9.0, 4.1 Hz, 1H), 3.72 (s, 1H), 3.58 (m, 1H), 1.55 (m, 2H), 1.42 (s, 9H), 1.28 (m, 26H), 1.05 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H).



(2*S*,3*R*)-1-(2,3-di-*O*-Benzyl-4,6-*O*-benzylidene- α -D-galactopyranosyl)-2-(*N*-tert-butoxycarbonylamino)-3-(*O*-benzyl)-octadecan-1,3-diol (42**)**

Phenyl 4,6-*O*-benzylidene-1-thio- α -D-galactopyranoside (**43**) (0.330 g, 0.611 mmol) and (2*S*,3*R*)-2-(*N*-tert-butoxycarbonyl)amino-3-benzyloxy-octadecan-1,3-diol (**33**) (0.200 g, 0.407 mmol) were azeotroped in toluene. Silver triflate (0.021 g, 0.081 mmol) was separately azeotroped with toluene. The donor and acceptor were dissolved in DCM (8.6 mL) at $-40\text{ }^{\circ}\text{C}$ under N_2 with 4 Å molecular sieves. Silver triflate and NIS (0.137 g, 0.611 mmol) were added, and the reaction mixture was stirred at $-20\text{ }^{\circ}\text{C}$ for 5 d. The reaction was quenched with Et_3N (2 mL). The crude mixture was filtered through a celite pad. The celite pad was rinsed with DCM (20 mL), and the filtrate was concentrated under reduced pressure. The crude mixture was purified via flash column chromatography on silica gel (petroleum ether/EtOAc 85:15), which resulted in **44** as a yellow oil (0.113 g, 30%): $[\alpha]_D^{22} -68.4$ (c 1.61, DCM); IR (neat) 2923, 2853, 1741, 1099, 1050 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.52 (m, 3H), 7.42–7.26 (m, 17H), 5.47 (s, 1H), 4.95 (d, $J = 3.2$ Hz, 1H), 4.85 (m, 2H), 4.65 (d, $J = 11.9$ Hz, 1H), 4.49 (m, 2H), 4.20 (m, 2H), 4.08 (dd, $J = 10.0, 3.3$ Hz, 1H), 3.98 (m, 2H), 3.90 (m, 2H), 3.75 (m, 2H), 3.65 (m, 1H), 3.56 (m, 1H), 1.44 (s, 9H), 1.27 (m, 27H), 0.89 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 155.7, 139.0, 138.9, 138.7, 138.0, 129.6, 129.0, 128.5, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7, 126.5,

101.2, 99.7, 79.3, 76.8, 75.8, 74.8, 73.8, 72.3, 72.1, 69.6, 68.2, 63.1, 60.5, 53.1, 32.1, 31.0, 30.1, 29.9, 29.5, 28.6, 25.5, 22.9, 21.2, 14.4, 14.3; HRMS (ESI) for $C_{57}H_{80}NO_9$ ($M^+ + H$) m/z calcd: 922.5835. Found: 922.5873.

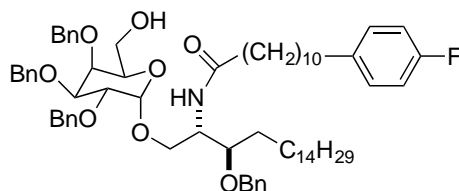


(2*S*,3*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)octadecan-1,3-diol (43**)**

(2*S*,3*R*)-1-(2,3-di-*O*-Benzyl-4,6-*O*-benzylidene- α -D-galactopyranosyl)-2-(*N*-*tert*-butoxycarbonylamino)-3-(*O*-benzyl)octadecan-1,3-diol (**42**) (0.050 g, 0.054 mmol) was vigorously stirred in DCM (0.5 mL). BH_3 -THF (0.270 mmol, 0.300 mL) was added at rt, stirring was continued for 45 min. $Sc(OTf)_3$ (0.005 g, 0.011 mmol) was then added and the reaction mixture stirred for 5 h. The reaction was quenched with MeOH (1 mL) and Et_3N (1 mL), and the mixture was concentrated in vacuo. The crude mixture was purified via flash column chromatography on silica gel (DCM/MeOH 95:5), which resulted in yellow oil **43** (0.115 g, 64%: $[\alpha]^{23}_D +40$ (c 0.08, DCM); IR (neat) 3374 (br), 2922, 2853, 1454, 1029 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 20H), 4.90 (d, $J = 3.3$ Hz, 1H), 4.77 (m, 1H), 4.71–4.55 (m, 5H), 4.45 (d, $J = 11.0$ Hz, 1H), 3.95 (m, 3H), 3.89 (m, 1H), 3.78 (m, 2H), 3.72 (m, 2H), 3.61 (m, 1H), 3.49 (m, 1H), 3.39 (m, 1H), 2.43 (br s, 2H), 1.61 (m, 4H), 1.23 (m, 25H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.1, 128.6, 128.6, 128.6, 128.2, 129.0, 129.0, 98.8, 76.2, 73.8, 72.7, 72.5, 70.9,

67.8, 66.0, 62.2, 53.3, 46.3, 37.7, 34.3, 32.1, 30.6, 29.9, 29.6, 25.4, 22.9, 22.5, 14.2;

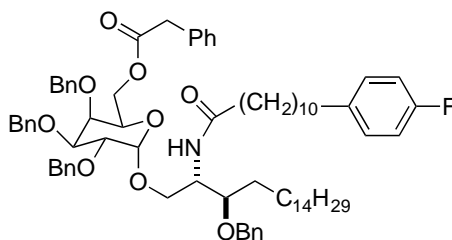
HRMS (ESI) for C₅₄H₇₄FNO₇ (M⁺ + H) *m/z* calcd: 824.5467. Found: 824.5462.



(2*S*,3*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3-diol (44**)**

(2*S*,3*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-octadecan-1,3-diol (**43**) (0.100 g, 0.121 mmol) was dissolved in pyridine (2.4 mL). PNP ester (0.140 g, 0.242 mmol) was added and the reaction stirred at rt overnight. The crude material was concentrated under reduced pressure and purified via flash column chromatography on silica gel (petroleum ether/EtOAc 60:40), which resulted in a white solid **44** (0.100 g, 73%): [α]_D²² –398 (*c* 0.26, DCM); IR (neat) 3317 (br), 2923, 2853, 1027 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (m, 20H), 7.11 (m, 2H), 6.95 (m, 2H), 5.76 (d, *J* = 9.1 Hz, 1H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.81 (dd, *J* = 11.7, 8.7 Hz, 2H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.64 (dd, *J* = 11.8, 9.7 Hz, 2H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.65 (d, *J* = 9.7 Hz, 1H), 4.63 (d, *J* = 9.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.32 (m, 1H), 4.04 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.87 (m, 2H), 3.85 (dd, *J* = 9.9, 2.7 Hz, 1H), 3.71 (m, 2H), 3.68 (m, 1H), 3.51 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.45 (m, 1H), 1.97 (m, 2H), 1.53 (m, 6H), 1.25 (m, 38H), 0.89 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 161.3 (*d*_{C-F}, *J* = 240.9 Hz), 138.8, 138.6 (*d*_{C-F}, *J* = 2.9 Hz),

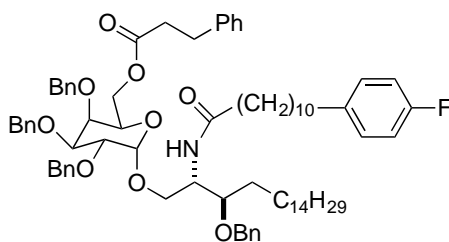
138.4, 129.8 (d_{C-F} , $J = 7.5$ Hz), 128.7, 128.6, 128.2, 128.0, 127.9, 127.8, 127.6, 115.1 (d_{C-F} , $J = 20.9$ Hz), 100.3, 80.0, 79.4, 76.9, 75.1, 74.7, 73.7, 73.5, 72.4, 71.4, 69.0, 62.7, 51.8, 37.1, 35.3, 32.1, 31.8, 31.1, 30.0, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 25.9, 25.6, 22.9, 14.3; HRMS (ESI) for $C_{69}H_{97}FNO_8$ ($M^+ + H$) m/z calcd: 1086.7198. Found: 1086.7168.



(2*S*,3*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl-6-phenylacetoyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,-diol (45a**)**

(2*S*,3*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)octadecan-3-(*O*-benzyl)-1,3-diol (**44**) (0.030 g, 0.028 mmol) was dissolved in DCM (2.8 mL). Phenylacetic acid (0.005 g, 0.034 mmol) and DMAP (0.001 g, 0.006 mmol) were added and the reaction stirred at rt for 5 min. DCC (0.006 g, 0.030 mmol) dissolved in DCM (0.5 mL) was added to the reaction and the mixture stirred at rt overnight. The crude mixture was concentrated *in vacuo* and purified via flash column chromatography on silica gel (petroleum ether/EtOAc 70:30), which resulted in a clear, colorless oil **45a** (0.027 g, 79%): $[\alpha]^{22}_D +7.6$ (c 0.10, DCM); IR 2923, 2853, 1455, 1096 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 25H), 7.10 (m, 2H), 6.95 (m, 2H), 5.75 (d, $J = 8.6$ Hz, 1H), 4.87 (m, 2H), 4.79 (d, $J = 8.9$ Hz, 1H), 4.77 (d, $J = 8.8$ Hz, 1H), 4.71 (d, $J = 11.7$ Hz, 1H), 4.62 (d, $J = 11.7$ Hz, 1H), 4.54 (d, $J = 11.6$ Hz, 1H), 4.44 (dd, $J = 11.2, 3.8$ Hz, 1H), 4.21

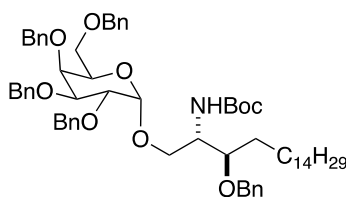
(m, 1H), 4.18 (m, 1H), 4.07–4.00 (m, 2H), 3.89 (m, 1H), 3.84 (dd, $J = 10.4, 2.6$ Hz, 1H), 3.75 (m, 1H), 3.68 (m, 2H), 3.57 (m, 3H), 2.55 (t, $J = 7.6$ Hz, 2H), 2.00 (m, 4H), 1.53 (m, 6H), 1.24 (m, 35H), 0.88 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.9, 171.2, 138.8, 138.7, 138.6, 138.4, 134.0, 129.8 ($d_{\text{C-F}}$, $J = 7.7$ Hz), 129.5, 128.8, 128.6, 128.5, 128.5, 128.0, 127.9, 127.8, 127.6, 127.4, 115.0 ($d_{\text{C-F}}$, $J = 20.9$ Hz), 100.0, 79.0, 78.9, 76.7, 74.8, 73.7, 73.3, 72.3, 68.9, 67.6, 63.8, 51.4, 45.6, 45.4, 41.6, 41.4, 37.7, 37.3, 37.0, 35.3, 34.3, 33.0, 32.1, 31.8, 31.0, 30.6, 30.2, 30.1, 29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.4, 27.8, 27.6, 27.3, 25.9, 25.5, 24.7, 22.9, 22.8, 22.5, 21.6, 20.7, 19.9, 19.8, 14.3; HRMS (ESI) for $\text{C}_{77}\text{H}_{103}\text{FNO}_9$ ($\text{M}^+ + \text{H}$) m/z calcd: 1204.7617. Found: 1204.7574.



(2S,3R)-2-Amino-(2,3,4-tri-O-benzyl-6-hydrocinnamoyl- α -D-galactopyranosyl)-3-(O-benzyl)-N-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,-diol (45b**)**

(2S,3R)-2-Amino-1-(2,3,4-tri-O-benzyl- α -D-galactopyranosyl)-3-(O-benzyl)-N-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,-diol (**44**) (0.030 g, 0.028 mmol) was dissolved in DCM (2.8 mL). Hydrocinnamic acid (0.005 g, 0.03 mmol) and DMAP (0.001 g, 0.006 mmol) were added and the reaction stirred at rt for 5 min. DCC (0.006 g, 0.03 mmol) dissolved in DCM (0.5 mL) was added to the reaction and the mixture stirred at rt overnight. The crude mixture was concentrated *in vacuo* and purified via flash column

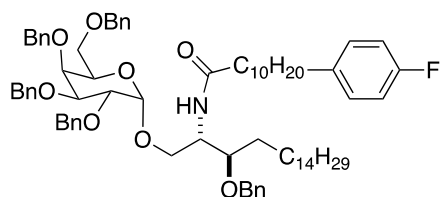
chromatography on silica gel (petroleum ether/EtOAc 70:30), which resulted in a clear, colorless oil **45b** (0.032 g, 94%): $[\alpha]_D^{25} +10$ (c 0.08, DCM); IR (neat) 2924, 2854, 1733, 1455, 1099 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.15 (m, 25H), 7.10 (m, 2H), 6.96 (m, 2H), 5.81 (d, $J = 8.7$ Hz, 1H), 4.93 (d, $J = 11.4$ Hz, 1H), 4.85 (m, 1H), 4.80 (d, $J = 9.4$ Hz, 1H), 4.76 (d, $J = 4.6$ Hz, 1H), 4.72 (m, 1H), 4.64 (d, $J = 11.8$ Hz, 1H), 4.57 (d, $J = 6.6$ Hz, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 4.43 (d, $J = 1.6$ Hz, 1H), 4.22 (m, 1H), 4.15 (dd, $J = 11.2$, 7.0 Hz, 1H), 4.06–4.02 (m, 2H), 3.89–3.84 (m, 2H), 3.79 (m, 1H), 3.72 (m, 2H), 3.58 (m, 1H), 2.97 (m, 3H), 2.89 (t, $J = 7.7$ Hz, 2H), 2.69 (m, 3H), 2.55 (m, 4H), 2.00 (m, 2H), 1.56 (m, 6H), 1.24 (m, 32H), 0.89 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.8, 173.1, 172.6, 161.2 ($d_{\text{C-F}}$, $J = 254.9$ Hz), 140.5, 140.4, 138.8, 138.6 ($d_{\text{C-F}}$, $J = 4.1$ Hz), 138.3, 129.8 ($d_{\text{C-F}}$, $J = 7.7$ Hz), 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 127.8, 127.6, 126.5, 126.5, 115.0 ($d_{\text{C-F}}$, $J = 20.8$ Hz), 99.0, 79.0, 78.9, 76.8, 74.8, 73.6, 73.4, 72.3, 69.0, 67.8, 63.6, 51.5, 37.0, 35.7, 35.6, 35.3, 34.1, 34.0, 32.8, 32.1, 31.8, 31.0, 30.9, 30.8, 30.1, 29.9, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 26.4, 25.9, 25.7, 25.5, 24.9, 22.9, 14.3; HRMS (ESI) for $\text{C}_{78}\text{H}_{105}\text{FNO}_9$ ($\text{M}^+ + \text{H}$) m/z calcd: 1218.7773. Found: 1218.7717.



(2*S*,3*R*)-1-(2,3,4,6-tetra-*O*-Benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-2-(*N*-tert-butoxycarbonylamino)octadecan-1,3-diol (46**)**

Phenyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl- α -D-galactopyranosyl)-3,4,6-tri-*O*-benzyl-1-thio- β -D-galactopyranoside **17** (0.203 g, 0.321 mmol) and (2*S*,3*R*)-2-(*N*-tert-butoxycarbonyl)amino-3-(*O*-benzyl)-octadecan-1,3-diol **33** (0.105 g, 0.234 mmol) were azeotroped with toluene. Silver triflate (0.012 g, 0.047 mmol) was separately azeotroped with toluene. The donor and acceptor were dissolved in DCM (11.7 mL) at -40 °C under N₂. Silver triflate and NIS (0.072 g, 0.321 mmol) were added and the reaction mixture was stirred at -20 °C for 3 d. The reaction was quenched with Et₃N (1 mL). The crude mixture was filtered through a celite pad and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography on silica gel (petroleum ether/EtOAc 85:15), which resulted in **46** as a clear, colorless oil (0.083 g, 35%): $[\alpha]^{20}_{\text{D}} +194$ (*c* 0.7, DCM); IR (neat) 2942, 2853, 1715, 1101 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.23 (m, 25H), 5.03 (d, *J* = 8.8 Hz, 1H), 4.93 (d, *J* = 11.4 Hz, 1H), 4.86 (d, *J* = 3.6 Hz, 1H), 4.82 (m, 1H), 4.75 (m, 2H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.50 (m, 3H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.04 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.94 (m, 2H), 3.91 (m, 2H), 3.80 (dd, *J* = 11.9, 4.8 Hz, 1H), 3.71 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.58 (m, 1H), 3.50 (m, 2H), 1.43 (s, 9H), 1.26 (m, 28 H), 0.88 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz CDCl₃) δ 138.8, 128.5, 128.4, 128.0, 128.0, 128.0,

127.7, 127.7, 99.2, 79.1, 78.7, 77.4, 75.2, 74.9, 73.7, 73.5, 73.2, 73.0, 72.2, 70.8, 70.4, 69.9, 69.2, 32.1, 30.8, 30.1, 29.9, 29.6, 28.6, 28.0, 26.7, 25.9, 22.9, 14.3; HRMS (ESI) for $C_{64}H_{88}NO_9$ ($M + H$)⁺ m/z calcd: 1014.6461. Found: 1014.6448.

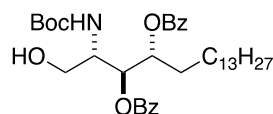


(2*S*,3*R*)-2-Amino-1-(2,3,4,6-tetra-*O*-benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3-diol (47**)**

(2*S*,3*R*)-1-(2,3,4,6-tetra-*O*-Benzyl- α -D-galactopyranosyl)-3-(*O*-benzyl)-2-(*N*-tert-butoxycarbonylamino)octadecan-1,3-diol **46** (0.029 g, 0.029 mmol) was dissolved in DCM (0.2 mL) at rt. TFA (0.992 mmol, 0.70 mL) was added dropwise. After 30 min, the reaction was concentrated under reduced pressure. The crude material was dissolved in DCM (5 mL), and washed with $NaHCO_3(aq)$ (5 mL). The organic phase was dried over $MgSO_4$, concentrated *in vacuo*, and was used directly in the next step.

The glycolipid (0.020 g, 0.02 mmol) and **27** (0.015 g, 0.026 mmol) were combined in pyridine (0.5 mL) and allowed to stir at rt overnight. The solution was concentrated under reduced pressure and the resulting crude material was purified via flash chromatography on silica gel (petroleum ether/EtOAc 85:15) to give **47** as a waxy solid (0.011 g, 35%): $[\alpha]^{20}_D +24$ (c 0.18, DCM); IR (neat) 2922, 2852, 1508, 1043, 695 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.23 (m, 25H), 7.10 (m, 2H) 6.94 (m, 2H), 6.05 (d, J = 8.8 Hz, 1H), 4.92 (d, J = 11.5 Hz, 1H), 4.82 (d, J = 3.2 Hz, 1H), 4.79 (m, 1H), 4.74 (t, J = 11.4 Hz, 2H), 4.64

(d, $J = 11.8$ Hz, 1H), 4.55 (t, $J = 11.3$ Hz, 2H), 4.46 (dd, $J = 11.8, 9.8$ Hz, 2H), 4.37 (d, $J = 11.8$ Hz, 1H), 4.16 (m, 1H), 4.02 (dd, $J = 9.8, 3.1$ Hz, 1H), 3.95 (dd, $J = 11.0, 5.1$ Hz, 1H), 3.88 (m, 3H), 3.67 (dd, $J = 11.0, 3.8$ Hz, 1H), 3.56 (m, 1H), 3.51 (dd, $J = 9.3, 6.6$ Hz, 1H), 3.38 (dd, $J = 9.3, 5.8$ Hz, 1H), 2.55 (t, $J = 7.6$ Hz, 2H), 1.98 (m, 2H), 1.54 (m, 6H), 1.23 (m, 38H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz CDCl_3) δ 173.1, 161.3 ($\text{d}_{\text{C-F}}$, $J = 241.3$ Hz), 138.8 ($\text{d}_{\text{C-F}}$, $J = 2.4$ Hz), 138.7, 138.7, 137.9, 129.8 ($\text{d}_{\text{C-F}}$, $J = 7.9$ Hz), 128.6, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.7, 126.3, 115.8, 115.1 ($\text{d}_{\text{C-F}}$, $J = 20.9$ Hz), 99.8, 79.0, 78.4, 77.4, 75.1, 74.9, 73.7, 73.6, 73.2, 72.8, 72.4, 72.2, 70.2, 70.0, 69.6, 69.3, 51.7, 36.9, 35.3, 32.1, 31.8, 30.9, 30.2, 29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.4, 25.8, 25.35, 25.2, 22.9, 14.3; HRMS (ESI) for $\text{C}_{76}\text{H}_{103}\text{FNO}_8$ ($\text{M} + \text{H}$) $^+$ m/z calcd: 1176.7670.

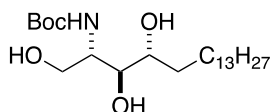


Found: 1176.7661.

(2S,3S,4R)-2-Amino-(*N*-tert-butoxycarbonyl)-octadecan-3,4-(*O*-dibenzoyl)-1,3,4-triol (48b)

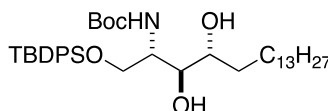
(2S,3S,4R)-2-(*N*-tert-Butoxycarbonylamino)-3,4-(*O*-dibenzoyl)-1-(*O*-tert-butylphenylsilyl)octadecan-1,3,4-triol (**52**) (0.700 g, 0.810 mmol) was dissolved in dry MeOH (7.4 mL) at 0 °C. TFA (14.7 mL) was added dropwise and the reaction stirred for 2 h. The solution was evaporated to dryness and co-evaporated with toluene 3 times. The residue was dissolved in dioxane (22 mL) and saturated NaHCO_3 (aq) (22 mL). Na_2CO_3 (0.232 g, 2.187 mmol) and Boc_2O (0.495, 2.27 mmol) were added and stirred overnight. This solution was extracted with EtOAc (50 mL). The organic phase was washed brine (50 mL), dried with

MgSO₄, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography on silica gel (Hexanes/EtOAc 80:20) to give **48b** (0.203 g, 40% over 2 steps) as a colorless oil.⁵⁴ ¹H NMR (400MHz, CDCl₃) δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.1 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 5.50 (d, *J* = 9.6 Hz, 1H), 5.40 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.05 (m, 1H), 3.64 (m, 2H), 2.60 (m, 1H), 1.99 (m, 2H), 1.48 (s, 9H), 1.27 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 3H).



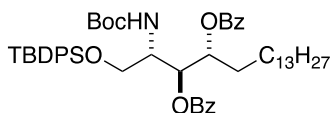
***tert*-Butyl [(2*R*,3*S*,4*S*)-1,3,4-trihydroxyoctadecan-2-yl]carbamate (**49**)**

Phytosphingsine (**20**) (3.00 g, 9.45 mmol) was added to THF (95 mL). Et₃N (3.8 mL) was added followed by Boc₂O (2.47 g, 11.3 mmol). The reaction mixture was stirred at rt overnight and was concentrated under reduced pressure. The crude material of **49** was carried over to the next step:⁵⁵ ¹H NMR (400 MHz, CDCl₃) δ 5.30 (m, 1H), 3.92 (m, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.68 (m, 1H), 3.62 (m, 1H), 3.29 (d, *J* = 6.9 Hz, 1H), 2.98 (m, 1H), 2.42 (d, *J* = 4.0 Hz, 1H), 1.52 (m, 2H), 1.45 (s, 9H), 1.29 (m, 24H), 0.88 (t, *J* = 6.9 Hz, 3H).



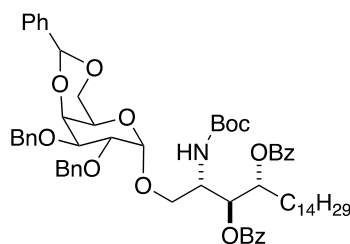
(2S,3S,4R)-1-(tert-Butyldiphenylsilyloxy)-2-[N-(tert-butyloxycarbonyl)amino]octadecan-3,4-diol (51**)**

tert-Butyl[(2*R*,3*S*,4*S*)-1,3,4-trihydroxyoctadecan-2-yl]carbamate was dissolved in 1:1 DCM/DMF (1:1 v/v, 20 mL). Et₃N (1.8 mL), DMAP (0.090 g, 0.080 mmol), and TBPDSO (11.7 mmol, 3.0 mL) were added at 0 °C, and the solution was stirred at rt overnight. It was then diluted with EtOAc (50 mL), and the solution was washed with brine (5 x 40 mL). The organic phase was dried over MgSO₄ and concentrated *in vacuo*. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 10:1) afforded (2*S*,3*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-[N-(*tert*-butyloxycarbonyl)amino]octadecan-3,4-diol (**51**) (4.75 g, 77% over 2 steps) as a colorless oil:⁵⁶ ¹H NMR (CDCl₃, 400 MHz) δ 7.65 (m, 4H), 7.42 (m, 6H), 5.17 (d, *J* = 8.4 Hz, 1H), 3.98 (m, 1H), 3.82 (m, 2H), 3.62 (m, 2H), 3.11 (d, *J* = 6.9 Hz, 1H), 2.62 (br s, 1H), 1.69 (m, 1H), 1.51 (m, 2H), 1.41 (s, 9H), 1.25 (s, 23H), 1.06 (s, 9H), 0.87 (t, *J* = 6.6 Hz, 3H).



(2S,3S,4R)-1-(tert-Butyldiphenylsilyloxy)-2-[N-(tert-butyloxycarbonyl)amino]octadecan-3,4-dibenzoate (52**)**

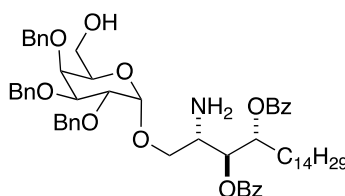
(2S,3S,4R)-1-(*tert*-Butyldiphenylsilyloxy)-2-[N-(*tert*-butyloxycarbonyl)amino]octadecan-3,4-diol (**51**) (0.481 g, 0.733 mmol) was dissolved in pyridine (7.8 mL). DMAP (0.010 g, 0.084 mmol) was added and the solution stirred at rt. BzCl (5.1 mmol, 0.60 mL) was added dropwise, and the solution was stirred overnight. The excess BzCl was slowly quenched with cold water, and the solution was then extracted with DCM (3 x 15 mL). The organic extracts were combined and dried (MgSO₄). The solution was concentrated under reduced pressure, and the crude product was purified via flash column chromatography on silica gel (hexanes/EtOAc, 95:5) to yield (2S,3S,4R)-1-(*tert*-butyldiphenylsilyloxy)-2-[N-(*tert*-butyloxycarbonyl) amino]octadecan-3,4-dibenzoate (**52**) as a colorless oil (0.531 g, 84% yield).⁵⁴ ¹H NMR (CDCl₃, 300 MHz) δ 7.96 (d, *J* = 8.0 Hz, 4H), 7.59 (m, 3H), 7.51 (m, 4H), 7.41 (m, 4H), 7.31 (m, 3H), 7.13 (m, 2H), 5.69 (dd, *J* = 9.6, 2.8 Hz, 1H), 5.49 (m, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.19 (m, 1H), 3.71 (m, 2H), 1.87 (m, 2H), 1.48 (s, 9H), 1.23 (m, 24 H), 1.00 (s, 9H), 0.88 (t, *J* = 6.6 Hz, 3H).



(2*S*,3*S*,4*R*)-2-Amino-3,4-(di-*O*-benzoyl)-1-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene- α -D-galactopyranosyl)(*N*-*tert*-butoxycarbonyl)octadecan-1,3,4-triol (53**)**

Benzyl-4,6-*O*-benzylidene-1-thio- β -D-galactopyranoside (**42**) (0.338 g, 0.624 mmol) and (2*S*,3*S*,4*R*)-2-amino-3,4-(di-*O*-benzoyl)(*N*-*tert*-butoxycarbonyl)octadecan-1,3,4-triol (**48b**) (0.261 g, 0.416 mmol) were azeotroped with toluene (3 x 5 mL) and left under vacuum overnight. Silver triflate (0.021 g, 0.083 mmol) was also azeotroped with toluene (1 mL) and left under vacuum overnight. Compounds **42** and **48b** were then combined in DCM (8.9 mL) with activated molecular sieves and cooled to $-20\text{ }^{\circ}\text{C}$. Silver triflate and NIS (0.140 g, 0.624 mmol) were added and the reaction mixture stirred at $-20\text{ }^{\circ}\text{C}$ for 3 d. Et₃N (2 mL) was added, and the reaction mixture was filtered through celite. The celite pad was rinsed with DCM (3 x 10 mL). The crude mixture was concentrated under reduced pressure and purified via flash column chromatography on silica (hexanes/EtOAc, 5:1) to yield **53** as a light yellow oil (0.201 g, 45% yield). $[\alpha]_{\text{D}}^{22} +55.0$ (c 1.50, DCM); IR (neat) 2924, 2853, 1716, 1261, 1097 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 8.07–7.95 (m, 5H), 7.59–7.29 (m, 17H), 7.18 (m, 3H), 5.61 (dd, J = 9.6, 3.8 Hz, 1H), 5.46 (s, 1H), 5.40 (m, 2H), 4.87 (d, J = 3.4 Hz, 1H), 4.74–4.61 (m, 4H), 4.25 (m, 2H), 4.17 (d, J = 3.0 Hz, 1H), 4.03 (dd, J = 10.2, 3.4 Hz, 1H), 3.99 (m, 1H), 3.91 (dd, J = 10.2, 3.3 Hz, 1H), 3.82 (dd, J = 10.8, 4.5 Hz, 1H), 3.75 (m, 2H), 1.87 (m, 2H), 1.47 (s, 9H), 1.27 (m,

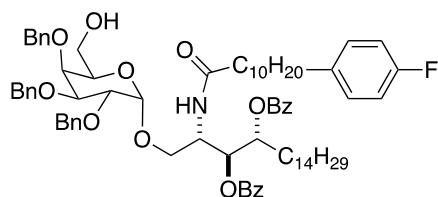
24H), 0.89 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 165.2, 165.4, 155.5, 138.9, 138.6, 137.9, 133.3, 133.0, 130.2, 130.1, 129.9, 129.8, 129.8, 129.7, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 126.3, 100.9, 100.2, 79.9, 75.9, 75.7, 74.7, 73.9, 73.5, 73.1, 72.1, 69.5, 63.4, 60.4, 50.7, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 28.4, 25.6, 22.9, 14.3; HRMS (ESI) for $\text{C}_{64}\text{H}_{81}\text{NNaO}_{12}$ ($\text{M} + \text{Na}$) $^+$ m/z calcd: 1078.5656. Found: 1078.5389.



(2S,3S,4R)-2-Amino-3,4-(di-O-benzoyl)-1-(2,3,4-tri-O-benzyl- α -D-galactopyranosyl) octadecan-1,3,4-triol (54**)**

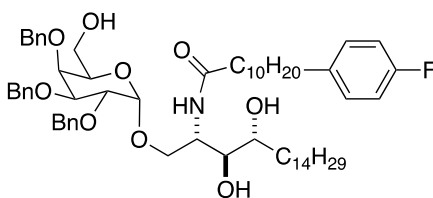
(2S,3S,4R)-2-Amino-3,4-(di-O-benzoyl)-1-(2,3-di-O-benzyl-4,6-O-benzylidene- α -D-galactopyranosyl)(*N*-*tert*-butoxycarbonyl)octadecan-1,3,4-triol (**53**) (0.090 g, 0.085 mmol) was stirred vigorously in DCM (0.8 mL). Borane tetrahydrofuran complex (0.425 mmol, 0.4 mL) was added, and the solution was stirred at rt for 45 min. Scandium triflate (0.006 g, 0.013 mmol) was added, and stirring was continued at rt until the starting material was consumed (monitored by TLC). The crude mixture was concentrated under reduced pressure, and the residue was purified via flash column chromatography on silica gel (hexanes/EtOAc 1:1) to yield (2S,3S,4R)-2-amino-3,4-(di-O-benzoyl)-1-(2,3,4-tri-O-benzyl- α -D-galactopyranosyl) octadecan-1,3,4-triol (**54**) as a colorless oil (0.060 g, 73% yield). $[\alpha]_D^{22} -52.8$ (c 1.20, DCM); IR (neat) 3305 (br), 2923, 2853, 1720, 1263, 1050

cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.7 Hz, 2H), 7.57 (m, 2H), 7.45–7.20 (m, 19H), 5.58 (ddd, *J* = 8.9, 4.6, 4.6 Hz, 1H), 5.48 (dd, *J* = 5.9, 5.9 Hz, 1H), 4.95 (d, *J* = 11.6 Hz, 1H), 4.84 (m, 1H), 4.75–4.69 (m, 2H), 4.62 (dd, *J* = 11.8, 4.7 Hz, 2H), 4.03 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.89 (m, 3H), 3.77 (dd, *J* = 6.0, 6.0, 1H), 3.70 (dd, *J* = 11.3, 6.6 Hz, 1H), 3.51 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.44 (m, 2H), 3.33 (m, 1H), 1.85 (m, 4H), 1.27 (m, 25H), 0.88 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 165.8, 138.9, 138.7, 138.4, 133.4, 133.3, 130.1, 130.0, 129.9, 129.9, 129.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 99.3, 79.2, 76.7, 75.2, 74.7, 73.7, 73.5, 71.4, 71.0, 70.8, 64.2, 62.5, 52.2, 32.1, 29.8, 29.7, 29.6, 29.5, 28.6, 26.7, 25.5, 22.8, 14.3; HRMS (ESI) for C₅₉H₇₆FNNaO₁₀ (M + Na)⁺ *m/z* calcd: 980.5288. Found: 980.5048.



(2*S*,3*S*,4*R*)-2-Amino-3,4-(di-*O*-benzoyl)-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)-octadecan-1,3,4-triol (55)

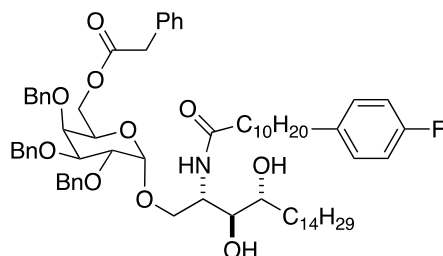
(2*S*,3*S*,4*R*)-2-Amino-3,4-(di-*O*-benzoyl)-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-octadecan-1,3,4-triol (**54**) (0.181 g, 0.189 mmol) was dissolved in pyridine (3.8 mL). 4-Nitrophenyl 11-(4-fluorophenyl)undecanoate **27** (0.219 g, 0.378 mmol) was added and the reaction stirred at rt overnight. The crude mixture was concentrated under reduced pressure and dissolved in DCM (10 mL). The organic phase was washed with 1M NaOH (3 x 15 mL) to removed excess PNP impurity and carried forward to the next step.



(2*S*,3*S*,4*R*)-2-Amino-*N*-(11-(4-fluorophenyl)undecanoyl)-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)octadecan-1,3,4-triol (56**)**

The crude material (2*S*,3*S*,4*R*)-2-amino-3,4-(di-*O*-benzoyl)-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (**55**) (0.047 g, 0.039 mmol) was dissolved in THF/MeOH (1:1 v/v, 3.8 mL). NaOMe (1M, 0.5 mL) was added dropwise and the reaction stirred at rt until starting material was completely consumed via TLC. The crude mixture was neutralized using DOWEX (C-211, H⁺, 16-50 mesh) resin. The resin was filtered and the filtrate was concentrated under reduced pressure to yield (2*S*,3*S*,4*R*)-2-amino-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)-octadecan-1,3,4-triol (**56**) as a yellow oil (0.036 g, 69% over 2 steps). $[\alpha]_D^{21} +53$ (c 0.36, DCM); IR (neat) 3318 (br), 2922, 2853, 1222, 1046 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.31 (m, 15H), 7.11 (m, 2H), 6.94 (m, 2H), 6.34 (m, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.89 (m, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.26 (m, 1H), 4.06 (dd, *J* = 9.8 Hz, 3.6 Hz, 1H), 3.87 (m, 2H), 3.82 (m, 2H), 3.67 (m, 4H), 3.45 (m, 4H), 2.56 (t, *J* = 7.5 Hz, 3H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.60 (m, 6H), 1.25 (m, 36H), 0.88 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 161.3 (d_{C-F}, *J* = 241.3 Hz), 138.6 (d_{C-F}, *J* = 2.7 Hz), 138.4, 138.2, 138.0, 129.8 (d_{C-F}, *J* = 7.7 Hz), 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 115.0 (d_{C-F}, *J* = 20.9 Hz), 99.2, 79.6, 76.4, 76.3, 74.7, 74.5, 74.4, 73.4, 73.3, 71.5,

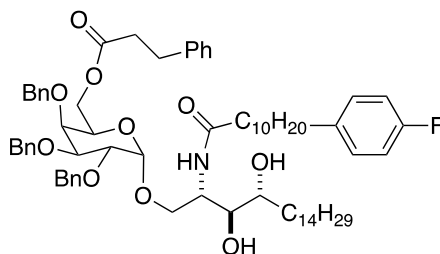
70.8, 69.7, 62.3, 51.6, 49.6, 37.0, 35.3, 34.3, 33.6, 32.1, 31.8, 29.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 26.7, 26.1, 25.9, 25.1, 22.9, 14.3; HRMS (ESI) for $C_{62}H_{91}FNNaO_9$ ($M + Na$)⁺ m/z calcd: 1034.6486. Found: 1034.6314.



(2*S*,3*S*,4*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl-6-phenylacetoyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)-octadecan-1,3,4-triol (57a**)**

(2*S*,3*S*,4*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)-octadecan-1,3,4-triol (**56**) (0.018 mg, 0.018 mmol) was dissolved in dry DCM (1.8 mL). DMAP (1 mg, 0.008 mmol) and phenylacetic acid (0.003 mg, 0.022 mmol) were added and the reaction stirred at rt for 5 min. DCC (0.004 mg, 0.019 mmol) was dissolved in dry DCM (0.5 mL) and added to the reaction flask, and the reaction stirred overnight. The crude mixture was concentrated under reduced pressure and purified via flash chromatography on silica gel (hexanes/EtOAc 70:30). (2*S*,3*S*,4*R*)-2-Amino-1-(2,3,4-tri-*O*-benzyl-6-phenylacetoyl- α -D-galactopyranosyl)-*N*-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (**57a**) was isolated as a white film (0.007 g, 20% yield). $[\alpha]^{21}_D$ -56 (c 0.14, DCM); IR (neat) 3326 (br), 2925, 2853, 1626 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.24 (m, 20H), 7.10 (m, 2H), 6.94 (m, 2H), 6.19 (d, J = 8.3 Hz, 1H), 4.86 (m, 2H), 4.76 (d, J = 11.7 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.4 Hz, 1H), 4.22 (m, 1H), 4.16 (m, 1H), 4.13 (d, J = 2.9 Hz, 1H), 4.09 (m, 2H), 4.03

(m, 1H), 3.79 (m, 2H), 3.74 (m, 2H), 3.57 (s, 2H), 3.46 (m, 4H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.14 (m, 2H), 1.93 (m, 4H), 1.70 (m, 4H), 1.25 (m, 28H), 0.86 (t, $J = 13.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 171.3, 162.2, 157.2, 138.6, 138.4, 138.3, 137.9, 129.8 ($d_{\text{C-F}}$, $J = 7.0$ Hz), 129.5, 128.7, 128.6, 128.6, 128.4, 128.3, 128.0, 127.7, 127.4, 115.1 ($d_{\text{C-F}}$, $J = 22.9$ Hz), 98.9, 79.4, 76.5, 76.0, 74.8, 74.4, 74.3, 73.1, 68.9, 63.8, 49.5, 45.7, 41.5, 36.9, 35.3, 34.1, 33.6, 32.1, 31.8, 29.9, 29.7, 28.0, 27.5, 25.8, 25.1, 22.9, 14.3; HRMS (ESI) for $\text{C}_{70}\text{H}_{96}\text{FNNaO}_{10}$ ($\text{M} + \text{Na}$) $^+$ m/z calcd: 1152.6905. Found: 1152.6727.



(2S,3S,4R)-2-Amino-1-(2,3,4-tri-O-benzyl-6-hydrocinnamoyl- α -D-galactopyranosyl)-N-(11-(4-fluorophenyl)undecanoyl)octadecan-1,3,4-triol (57b)

(2S,3S,4R)-2-Amino-1-(2,3,4-tri-O-benzyl- α -D-galactopyranosyl)-N-(11-(4-fluorophenyl)undecanoyl)-octadecan-1,3,4-triol (**56**) (0.018 mg, 0.018 mmol) was dissolved in dry DCM (1.8 mL). DMAP (0.001 mg, 0.008 mmol) and hydrocinnamic acid (0.003 mg, 0.022 mmol) were added and the reaction stirred at rt for 5 min. DCC (4 mg, 0.019 mmol) was dissolved in dry DCM (0.5 mL) and added to the reaction flask, and the reaction stirred overnight. The crude mixture was concentrated under reduced pressure and purified via flash chromatography on silica gel (hexanes/EtOAc 70:30). (2S,3S,4R)-2-Amino-1-(2,3,4-tri-O-benzyl-6-hydrocinnamoyl- α -D-galactopyranosyl)-N-(11-(4-fluorophenyl)undecan-

oyl)octadecan-1,3,4-triol (**57b**) was isolated as a white film (0.008 mg, 20% yield). $[\alpha]^{21}_{\text{D}} -31$ (c 0.18, DCM); IR (neat) 3348 (br), 2925, 2853, 1556, 1094 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.25 (m, 15H), 7.10 (m, 2H), 6.95 (m, 2H), 6.21 (d, $J = 8.3$ Hz, 1H), 4.92 (d, $J = 11.4$ Hz, 1H), 4.87 (m, 2H), 4.80 (d, $J = 11.8$ Hz, 1H), 4.75 (d, $J = 11.6$ Hz, 1H), 4.68 (d, $J = 11.6$ Hz, 1H), 4.54 (m, 1H), 4.24 (m, 1H), 4.12 (m, 1H), 4.06 (m, 1H), 4.04 (m, 2H), 3.80 (m, 4H), 3.55 (d, $J = 9.0$ Hz, 1H), 3.48 (m, 4H), 2.89 (t, $J = 7.8$ Hz, 2H), 2.56 (m, 4H), 2.14 (m, 3H), 1.93 (m, 2H), 1.71 (m, 2H), 1.25 (m, 36H), 0.88 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.0, 172.7, 161.3 ($\text{d}_{\text{C-F}}$, $J = 239.5$ Hz), 156.9, 140.6, 138.6 ($\text{d}_{\text{C-F}}$, $J = 2.7$ Hz), 138.4, 138.2, 137.9, 129.8 ($\text{d}_{\text{C-F}}$, $J = 7.8$ Hz), 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.6, 126.5, 115.1 ($\text{d}_{\text{C-F}}$, $J = 20.9$ Hz), 98.9, 79.5, 77.4, 76.4, 76.1, 74.8, 74.4, 74.3, 73.5, 73.3, 70.8, 69.7, 69.1, 63.5, 49.4, 36.9, 35.7, 35.3, 34.1, 33.6, 32.1, 31.8, 30.9, 30.4, 29.9, 29.7, 29.7, 29.6, 29.5, 29.4, 27.9, 27.5, 26.7, 26.1, 25.9, 25.8, 25.1, 22.9, 21.7, 14.3; HRMS (ESI) for $\text{C}_{71}\text{H}_{98}\text{FNNaO}_{10}$ ($\text{M} + \text{Na}$) $^+$ m/z calcd: 1166.7061. Found: 1166.6683.

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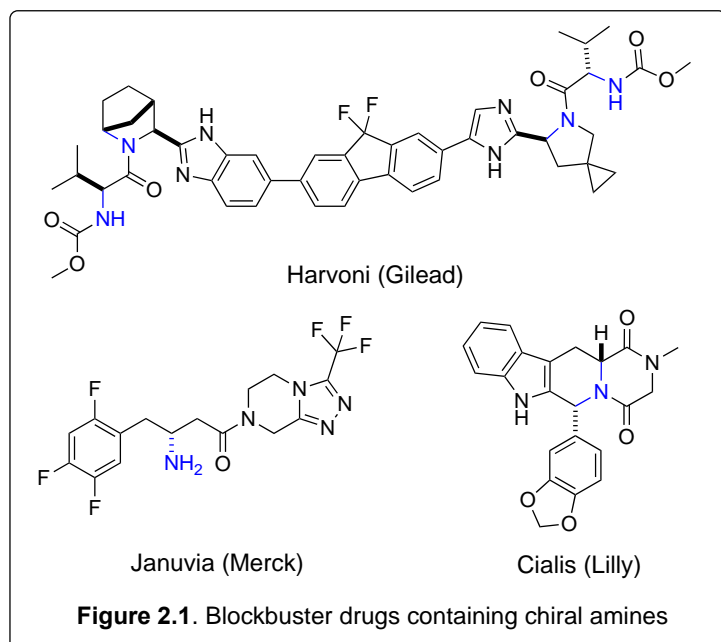
CHAPTER 2

Novel Reactions with Ketiminium Salts

2.1 INTRODUCTION

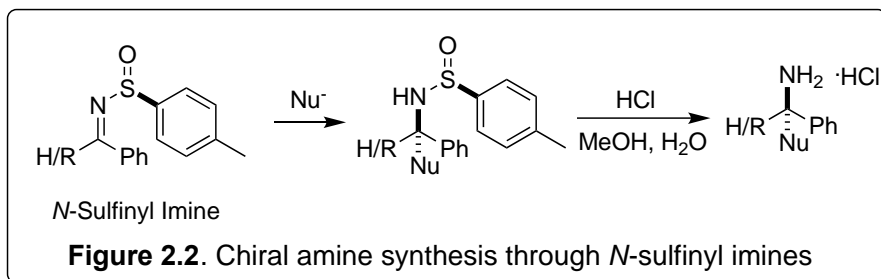
2.1.1 *N*-Sulfinyl Imines

Chiral amines are prevalent in many of the top-selling small, organic molecule drugs on the market. They can be found in blockbuster drugs such as Harvoni (Gilead), Januvia (Merck), and Cialis (Lilly) (Fig. 2.1). Therefore, a significant challenge was presented in developing an efficient asymmetric synthesis of such amines without the use of expensive



chiral and precious metal catalysts. The development of chiral *N*-sulfinyl imines seemed to solve this problem (Fig. 2.2). The work was pioneered by Franklin Davis who reported on the synthesis and utility of *p*-toluenesulfinyl imines.¹ This chiral auxiliary sulfinyl group is an ideal

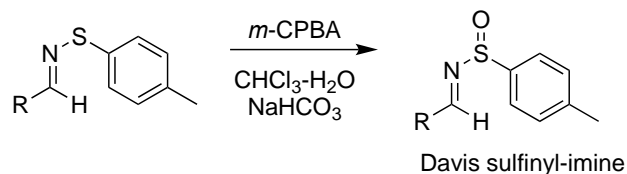
substituent because it activates the imine for nucleophilic addition while acting as a directing group for good to excellent facial selectivity. The sulfinyl group can also be easily removed after addition leaving a primary amine for further functionalization.



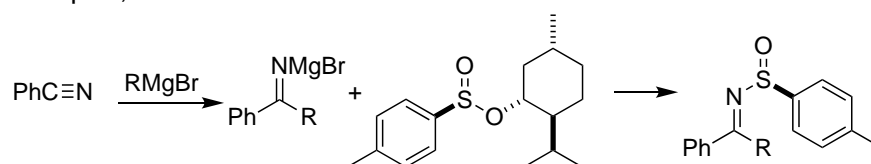
2.1.1.1 History of *N*-Sulfinyl Imine Development

The first racemic *N*-sulfinyl imines were reported by Davis, Friedman, and Kluger in 1974. This chemical species was achieved by oxidizing *N*-sulfenyl imines with *m*CPBA (Fig. 2.3a). Cinquini and Cozzi later reported the first enantio-pure synthesis of *p*-tolyl-*N*-sulfinyl imine via a Grignard reaction with a nitrile followed by reaction with a chiral sulfinate ester (Fig. 2.3b).² A major milestone in the field of *N*-sulfinyl imine chemistry came in 1997 when Ellman and co workers reported the first asymmetric synthesis of *tert*-butane sulfinamide (TBSA).³ Soon after, the Ellman group published a new method of enantioselectively generating *N*-sulfinyl aldimines and ketimines through a Lewis acid-mediated condensation reaction between a ketone or aldehyde and TBSA (Fig. 2.3c).⁴ The sulfinamide reagents are often referred to as the chemist who pioneered the work with them: *p*-toluene sulfinamide will be referred to as the Davis sulfinamide, and TBSA, the Ellman sulfinamide. Therefore, products of reactions with the sulfinamides will be referred to as Davis and Ellman, respectively.

a. Davis, 1974



b. Cinquini, 1977



c. Ellman, 1999

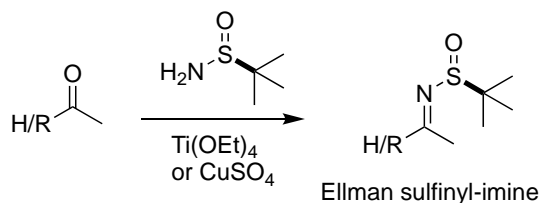
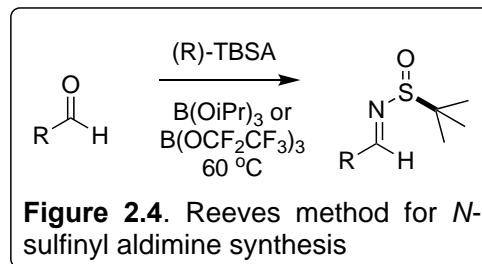


Figure 2.3. Methods of generating *N*-sulfinyl imines. **a.** first synthesis reported by Davis. **b.** first asymmetric synthesis reported by Cinquini. **c.** first asymmetric synthesis using TBSA reported by Ellman

Currently, the $\text{Ti}(\text{OEt})_4$ method is the most widely used for making both the Ellman and Davis sulfinyl-imine. One major drawback of the Ellman method is the use of stoichiometric amounts of $\text{Ti}(\text{OEt})_4$. Upon aqueous work up, the excess titanium reagent is converted to insoluble titanium oxide (TiO_2). Filtration of TiO_2 can be extremely slow and cumbersome specifically on the large scale required for industrial-sized drug synthesis. Recently, Reeves and co workers at Boehringer Ingelheim (BI) developed a new method of generating *N*-sulfinyl aldimines using borate reagents (Fig. 2.4).^{5,6} This method is useful for process scale synthesis of aldimines. Not only does it bypass the transition metal requirement, the reaction is run neat, and both the borate and sulfonamide reagent are

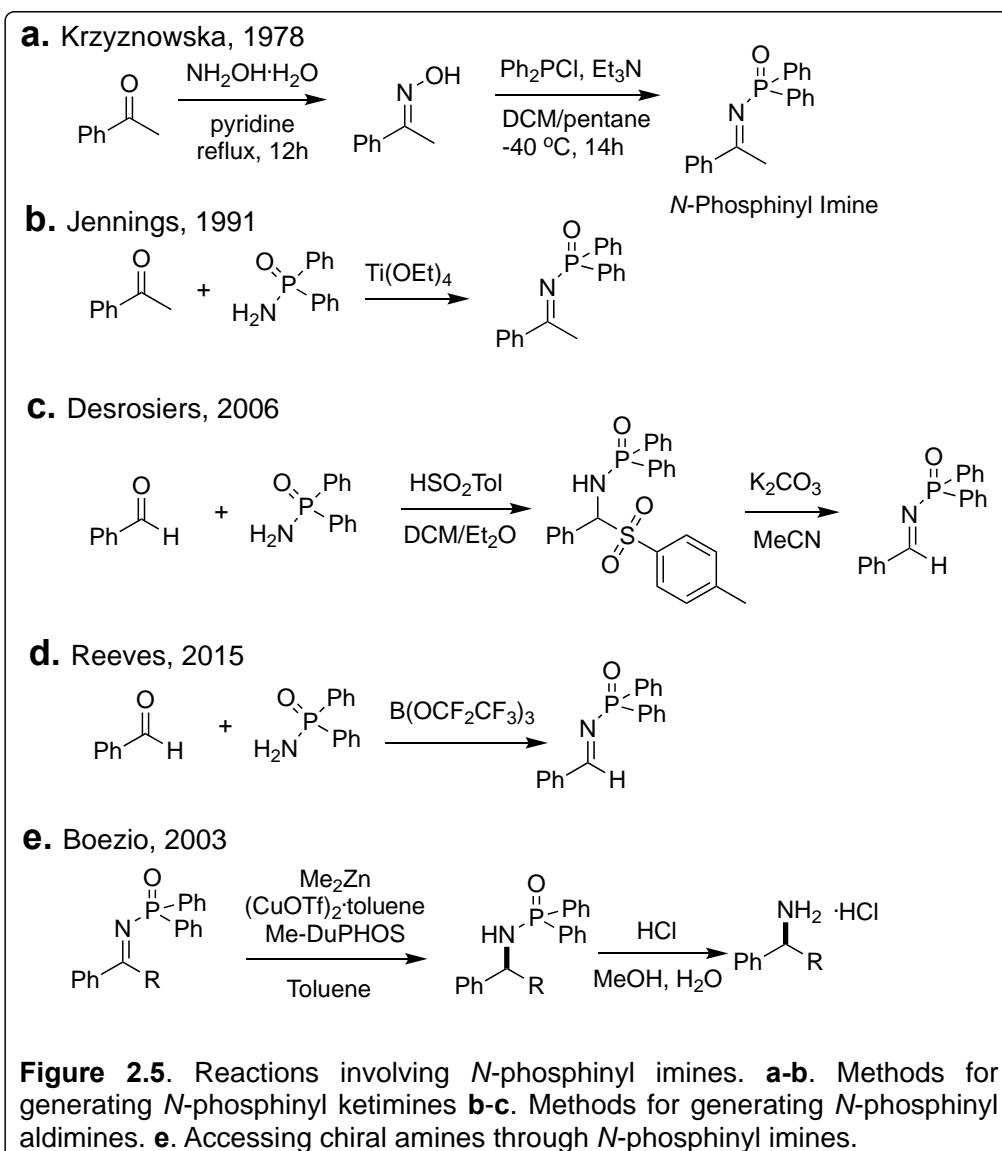


removed upon workup resulting in minimal purification. The only drawback with this process is that it is limited to *N*-sulfinyl aldimines; *N*-sulfinyl ketimines still require $\text{Ti}(\text{OEt})_4$. Interestingly, Reeves could employ the same borate reagents and condensation conditions to generate *N*-phosphinyl aldimines and *N*-tosyl aldimines. Once again, these reactions did not tolerate ketones. Therefore, the significant challenge of overcoming the titanium requirement for ketone condensation still persists.

2.1.2 *N*-Phosphinyl Imines

N-Phosphinyl imines are another set of synthetically useful imines. These compounds are of interest because they provide another method of generating chiral amines. These phosphinyl species are easy to use- because they are highly crystalline which makes purification simple. The phosphinyl group is similar to the sulfinyl in that it is also easily removed by forming the HCl salt while maintaining stereochemistry. The synthesis of these compounds however, is not trivial. The first process of generating *N*-phosphinyl ketimines was reported by Krzyznowska and Stec in 1978.⁷ It begins with a condensation between a ketone and hydroxylamine to form an oxime. Upon treatment with chlorodiphenylphosphine, an unstable *O*-phosphinyl oxime forms which undergoes a rearrangement to give the desired *N*-phosphinyl ketimine (Fig. 2.5a). Because oximes are high energy, and the reactive intermediate is not especially stable, this reaction process is not particularly popular in industrial settings. Following the Ellman method, *N*-phosphinyl ketimines can also be generated using $\text{Ti}(\text{OEt})_4$ (Fig. 2.5b).⁸ Like the sulfinyl imines, one must overcome the necessity of a titanium reagent to produce *N*-phosphinyl

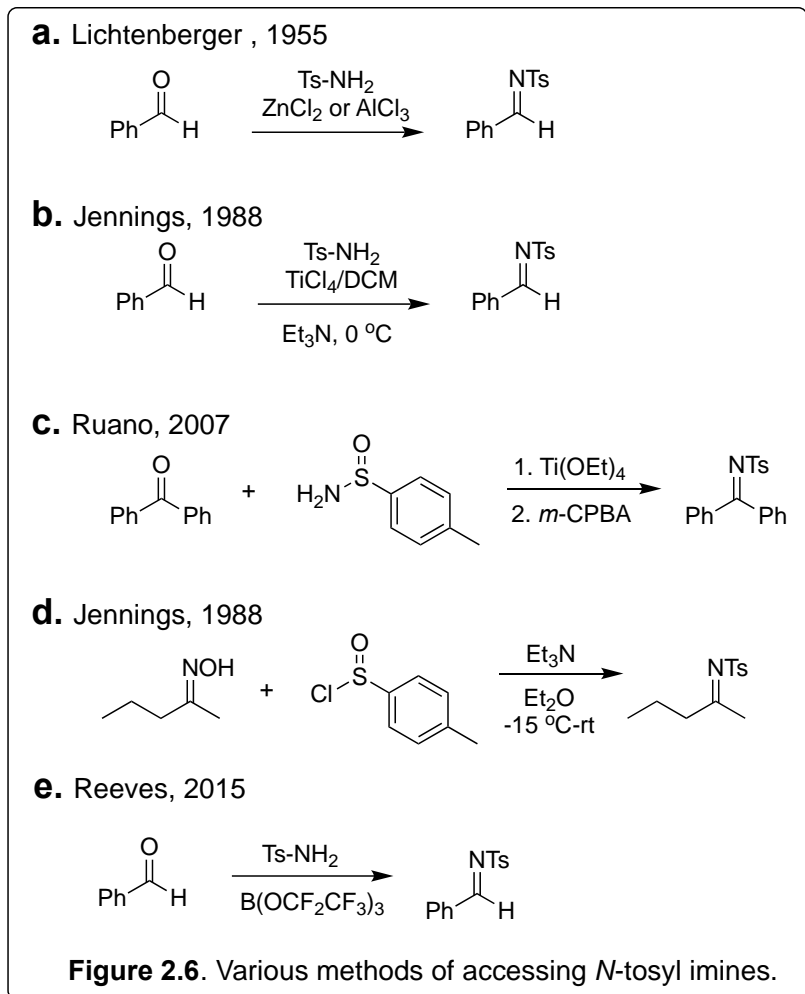
ketimines efficiently on large scales. One method for generating *N*-phosphinyl aldimines is a two-step process where condensation between an aldehyde and the phosphinamide occurs first with the addition of a tosyl group. The tosyl group is removed under basic conditions to establish the *N*-phosphinyl imine (Fig. 2.5c).⁹ The Reeves borate method overcomes the burden of the two step synthesis but is limited to aldehyde substrates (Fig 2.5d). Unlike the sulfinyl imines, the phosphinyl imines are not chiral. The asymmetry is induced through nucleophilic addition in the presence of a chiral catalyst, usually with a PHOS-type ligand (Fig. 2.5e).¹⁰



2.1.3 *N*-Toluenesulfonyl Imines

N-Toluenesulfonyl (tosyl) imines are synthetically useful intermediates that have been gaining more popularity.¹¹ Unlike *N*-acyl imines which have a tendency to polymerize, *N*-tosyl imines are much more stable and can be isolated and stored quite easily. The electron-withdrawing sulfonyl group activates the imines for nucleophilic addition similar to *N*-acyl imines. The Davis group has also pioneered additional reactions with *N*-tosyl imines by converting them to 2-sulfonyloxaziridines using peroxy acids in basic media. These species are useful neutral oxidants that can be used in a wide array of oxidation reactions.¹² Therefore, *N*-tosyl imines are an essential intermediate for these reactions. The first synthesis of *N*-tosyl imines was reported in 1955 by Lichtenberger and co workers.¹³ The one-step process involves a Lewis acid-mediated condensation between an aromatic aldehyde and *p*-toluene sulfonamide (Fig. 2.6a). This process is limited to aromatic aldehydes and therefore is not practical for many substrates. Decades later, Jennings and Lovely reported a titanium-mediated method of generating *N*-tosyl imines that is limited to aromatic and aliphatic aldehydes (Fig. 2.6b).¹⁴ Although they attempted such a reaction on ketones, they observed no imine product and instead isolated the aldol adduct. Another method of generating *N*-tosyl imines utilizes the Ellman protocol for *N*-sulfinyl imines using $\text{Ti}(\text{OEt})_4$ and then oxidizing the sulfinyl group to a sulfone using *m*-CPBA (Fig. 2.6c).¹⁵ Although this protocol is much more useful as it applies to aldehydes and ketones, it hasn't overcome the burden of removing titanium oxide in work up. Another proposed method involves reacting an oxime with *p*-toluenesulfinyl chloride. Similar to the reaction in Figure 2.5a, the reactive intermediate then undergoes a rearrangement to produce the *N*-tosyl imine (Fig. 2.6d).¹⁶ As with the *N*-phosphenyl

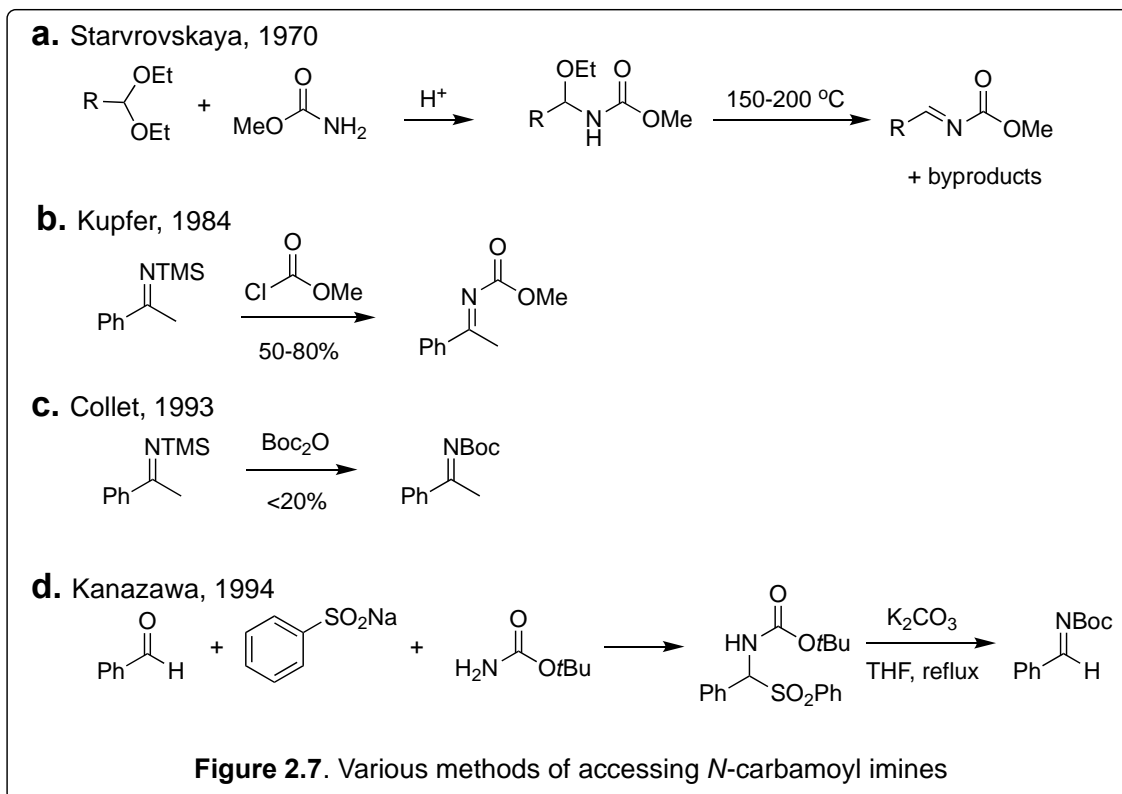
imines, these reactions are not preferred in large-scale reactors. As mentioned, the Reeves borate method can also generate *N*-tosyl imines but is limited to aldehyde substrates (Fig. 2.6e). Although there is a wealth of options for generating *N*-tosyl imines, each method is problematic in its own way.



2.1.4 *N*-Carbamoyl Imines

N-Carbamoyl imines (CBz-, Boc-protected imines) are another set of synthetically useful imine derivatives.¹⁷ Like the previously mentioned substituted imines, *N*-carbamoyl imines are activated for nucleophilic addition, and the carbamoyl protecting group can

easily be cleaved after addition. Cleavage of the carbamoyl group is arguably easier than the aforementioned imines in that the cation stabilization is stronger due to the greater availability of the nitrogen lone pair in the carbamate. Because they can be so reactive, one drawback of these compounds is that they are not stable for long-term storage and tend to be hygroscopic. *N*-carbamoyl imine synthesis is not trivial either. The first synthesis by Stravrovskaya in 1970 involved a reaction between diethylacetals and methyl carbamate (Fig. 2.7a).¹⁸ This method results in a mixture of the desired product and byproducts and was later improved upon by using silyl imines as the starting material.¹⁹ The synthesis, however, focused on methyl carbamates which are generally not used due to difficulties in later de-protection (Fig. 2.7b). This synthetic limitation was overcome by Collet and co workers in 1993 with the first reported synthesis of Boc-protected imines (Fig. 2.7c).²⁰ Although it was an impressive feat, the reaction is very low yielding. Today, the most popular method of generating *N*-carbamoyl imines is similar to an old method of generating *N*-phosphinyl imines (see Fig. 2.5b). Aromatic aldehydes react with benzenesulfinate and *tert*-butylcarbamate to form a highly stable intermediate *N*-(*tert*butoxycarbonyl)- α -phenylsulfonylbenzylamine. In the presence of heat and base, the benzenesulfinate is eliminated to form the *N*-carbamoyl aldimine (Fig. 2.7d).²¹ Although this method is the most promising in terms of yield and scale up, this two-step synthesis is inefficient (stoichiometric amounts of benzenesulfinate required) and is limited to aldehydes.

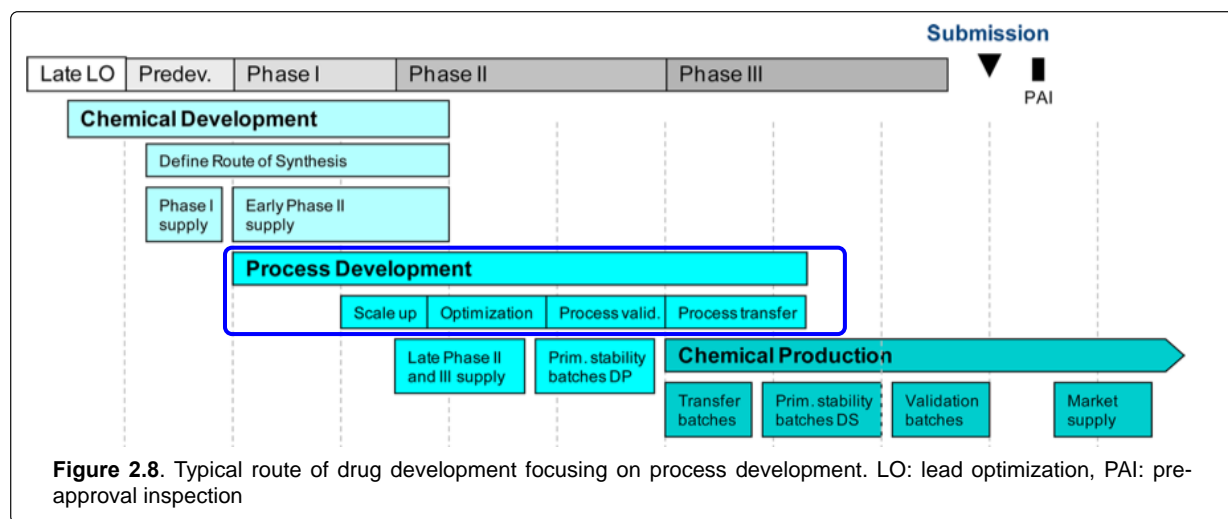


2.1.5 Goal: Develop a Process-Friendly Method of Generating Substituted Ketimines via Transimination

2.1.5.1 Parameters for Process Chemistry

Many of the disadvantages of the reactions mentioned involve low yield, scalability, and atom economy. In the timeline of drug development, an active pharmaceutical ingredient (API) is developed in a medicinal chemistry lab. The next step is to test the compound in toxicology studies, develop a viable formulation for administering the API, and subsequently testing the bioavailability, metabolism, safety and efficacy of the API in humans in clinical trials. The process chemistry lab takes over for large-scale synthesis of the API to support all of these activities (Fig. 2.8).²² Typically, medicinal chemistry synthetic routes cannot be scaled up in the process lab because the goal of medicinal

chemists is to make the API quickly on a small scale. A process chemist's goal is to make the API as efficiently as possible on a large scale. Although speed remains a priority throughout the pharmaceutical process, safety, quality control, and economics are also important parameters that must be considered.



Material cost is obviously a major factor in chemical development. Cheap starting materials such as commodity chemicals are ideal. Precious metal catalysts such as palladium reagents are avoided not just for cost considerations, but also safety regulations. When palladium is used in a reaction, proper precautions must be taken to ensure that no palladium contaminate persists in the product. Palladium removal methods have been developed to counter this issue, which unfortunately adds another step to the reaction sequence.^{23,24} Reaction time and temperature can also be costly factors. If a reaction must run overnight at 100 °C, a large reactor will require large amounts of energy to maintain the high temperature for the duration of the reaction.

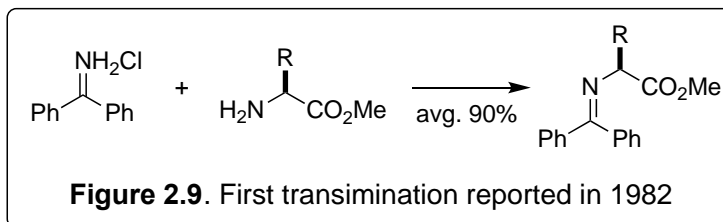
Another parameter to consider is atom economy and waste generation. Atom economy is a measure of the percent efficiency where the molecular mass of the desired product

is divided by the molecular mass of all of the reactants.²⁵ First introduced by Barry Trost in 1995, atom economy is considered a metric for how “green” a process is. Therefore, when considering the reaction sequence in Figure 2.7d, which is the most commonly used method of Boc-imine formation, the atom economy is 54% due to the addition then subsequent elimination of benzenesulfinate which doesn’t contribute to the mass of the final product. It also results in a stoichiometric amount of waste generated, which must be separated from the product and treated. One strategy to reduce waste is to run the reaction as concentrated as possible. Therefore, there is less solvent waste to handle. For example, the reaction in Figure 2.6e has an atom economy of 95%. It is also considered very green because the reaction is run neat, where no solvent is required, minimizing waste. Many little considerations can add up to an efficient drug campaign in process development.

2.1.5.2 Literature Precedent for Transimination

In 1982, Polt and O’Donnell reported the first application of transimination via ketiminium salts (Fig. 2.9).²⁶ The typical condensation between ketone and amine was not practical in this reaction due to concerns of epimerization. The reaction was, on average, very high yielding. It occurred at ambient temperature and required neither acid, base, nor any other additive. Although this method was reported for ketiminium salts with alkyl amines, it was worth exploring whether the reaction could occur with ketiminium salts and sulfinamides.

If successful, this method could bypass the titanium requirement in the Ellman method of generating *N*-sulfinyl ketimines.



Furthermore, if the synthesis of *N*-sulfinyl ketimines via transimination succeeded, it raises the question: could the same method be used for *N*-tosyl, -phosphinyl, and – carbamoyl imines? Although the electronics of an alkyl amine and sulfinamide are vastly different, it was appealing to investigate if transimination could occur on different substrates.

2.2 RESULTS AND DISCUSSION

2.2.1 Research Objectives

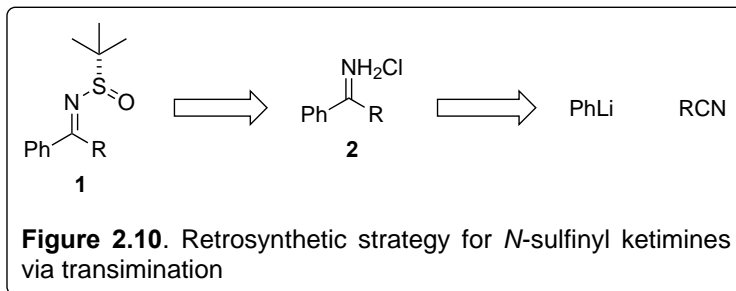
The goals of this study were to

1. Generate a library of ketiminium salts
2. Optimize the synthesis of *N*-sulfinyl ketimines via transimination with Ellman- and Davis-type sulfinamides
3. Use optimized reaction conditions to generate *N*-tosyl, -phosphinyl, and –carbamoyl ketimines

2.2.2 Synthesis of Ketiminium Library

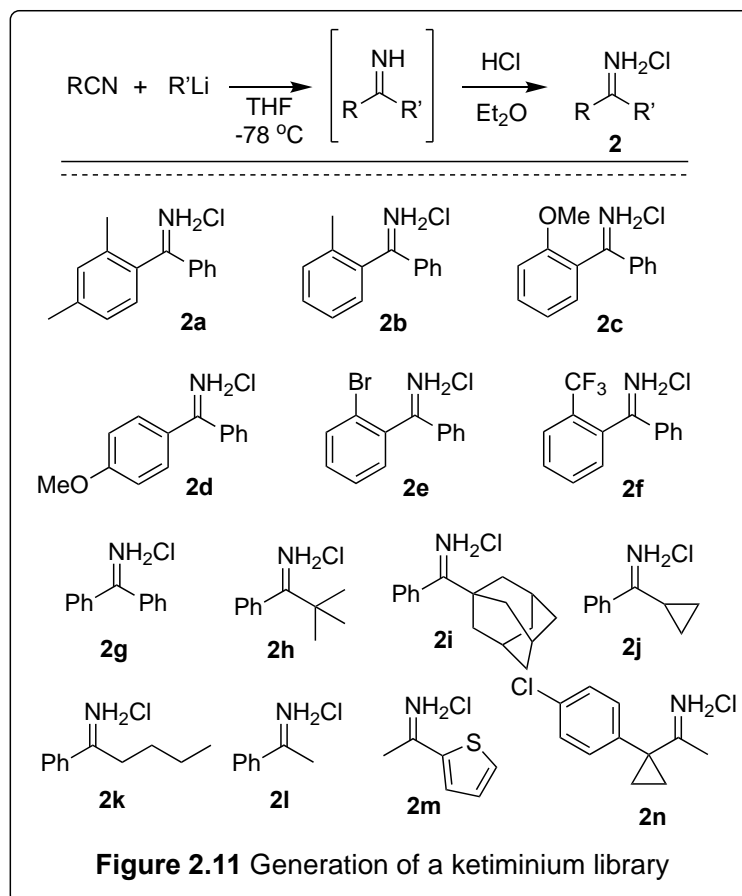
2.2.2.1 Retrosynthetic Strategy

The retrosynthesis of *N*-sulfinyl ketimines (1) is straightforward (Fig. 2.10). As mentioned, the plan was to access 1 via transimination with a ketiminium salt 2 and a commercially available sulfinamide. Following a known procedure, an iminium salt can be achieved via addition into a nitrile using an organolithium reagent followed by acidification.²⁷



2.2.2.2 Ketiminium Library

The synthesis of the HCl ketiminium salts followed the same protocol, changing the nitrile and organo-lithium reagent, with quantitative yields for the most part (Fig. 2.11).²⁷ Phenyllithium was added to the corresponding nitrile at -78 °C for 2a-j. *n*-Butyllithium was added to benzonitrile for 2k, and methyllithium was used for 2l-n. The compound library contained benzophenone imine-derived ketimines to observe the different effects due to



substitution on one phenyl group. Some parameters considered were the position (ortho versus para, or both ortho and para), the size (sterically bulky versus small), and the electronics (electron withdrawing versus donating) of the substituent. Another subset of ketiminium salts looked at the effect of aromatic versus alkyl substituents. The library contains salts that have one aromatic and one alkyl group on the imine (2h-m) and one doubly alkyl ketiminium salt (2n). The alkyl substituents were chosen specifically to monitor if the reaction works better with small alkyl groups versus sterically bulky substituents.

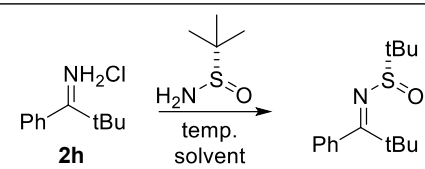
It was expected that the benzophenone-type ketimines and ketimines with smaller substituents would undergo transamination more easily. The ketiminium salt 2h was chosen as the first substrate for optimization. Because it contains *t*-butyl, the reaction might be hindered due to steric effects. Therefore, if the reaction could succeed with a less active substrate, the other ketiminium salts should react easily under the optimized conditions.

2.2.3 Solvent Screen

Because transamination occurs by stirring the iminium salt and sulfinamide together with no additives or catalysts, the solvent and temperature play an important role in the reaction. Therefore, the optimal solvent had to be chosen (Table 2.1). Each reaction was run on a 0.5 g scale with 1.2 eq. of (*S*)-TBSA with the reaction conversion monitored via high performance liquid chromatography (HPLC) every hour until the conversion stalled. The solvents chosen were polar aprotic, because protic solvents could solvolyze or hydrolyze the starting material salt (Entry 8). At room temperature,

the reactions proceeded very slowly, with less than 50% conversion for all solvents. Dichloromethane (DCM) and ethyl acetate (EtOAc) reaction conversions stalled at 45% and 35%, respectively (Entries 6 and 7). The reactions in *N*-methyl-2-pyrrolidone (DMP), 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU), and acetonitrile (MeCN) all produced a byproduct observed via HPLC that increased as the reaction continued. Therefore, dimethyl sulfoxide (DMSO) and dimethylformamide

Table 2.1 Solvent screen for transimination

			
Entry	solvent	temp.	% conv.
1	DMF	rt	<50
		60 °C	50
		80 °C	90
2	DMPU	rt	<50
3	DMP	rt	<50
4	DMSO	rt	<50
5	MeCN	rt	<50
6	DCM	rt	45
7	EtOAc	rt	35
8	MeOH	rt	0

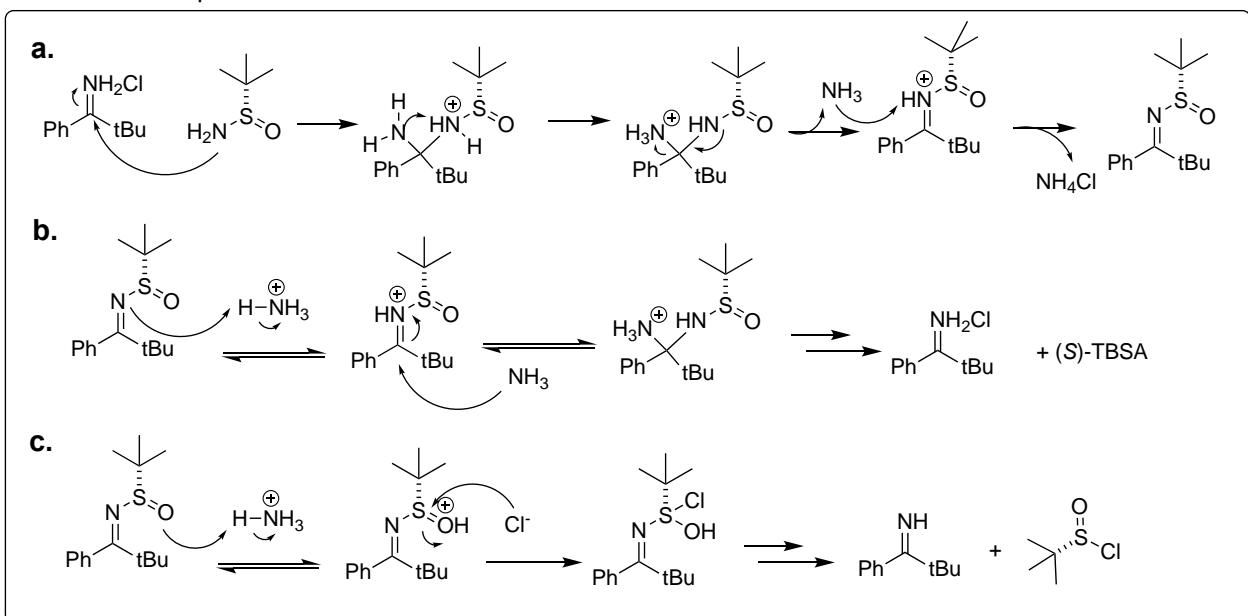
(DMF) were chosen as the best solvents. DMF was ultimately selected due to the ease of removal in workup. Even upon aqueous workup, DMSO was still present in the crude material (via ^1H NMR). Because the traditional Ellman method of generating *N*-sulfinyl ketimines with $\text{Ti}(\text{OEt})_4$ usually requires heat, the reaction in DMF was also heated (Entry 1). Upon heating the reaction mixture to 60 °C then 80 °C, the reaction conversion increased dramatically with 80 °C being the optimal temperature. Because process methods seek to reduce as much waste as possible, the ideal concentration of the reaction was also investigated under the described conditions. It was anticipated that more concentrated reactions would work better because the more dilute the reaction, the less the reactants can interact with each other. This hypothesis was confirmed when it was found that five volumes of DMF produced the best reaction

conversions. This means that if the reaction is run on a 0.5 g scale, 2.5 mL of DMF is used. Therefore, the reaction works best in five volumes DMF at 80 °C, with 1.2 eq. of sulfinamide. A strange observation was noted however, when the reaction was allowed to stir overnight, the conversion would dramatically decrease. It seemed as though something in the reaction was causing the desired product to decompose over time.

2.2.4 Ammonium Salt Assay

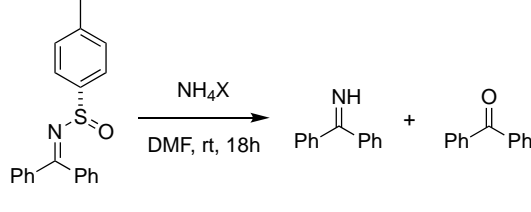
Due to the simplicity of the reaction, there aren't many components in the system that can destroy the desired product. When considering the mechanism, the only chemical present in the reaction other than the two starting materials and product, is ammonium chloride which is displaced in order to form the product (Scheme 2.1a, chloride ion not shown for clarity). Perhaps, the last step in the mechanism is reversible and ammonium chloride can add back into the desired product. If this were the case, an equilibrium between starting material and product would be established (Scheme 2.1b). In the worst-case scenario, the chloride ion from the ammonium chloride byproduct can add into the sulfinyl

Scheme 2.1 Proposed mechanism of transimination with TBSA



group, breaking the N-S bond in the product. If this were to happen, the free base imine and sulfinyl chloride would form.

Table 2.2 Ammonium salt assay

		
Entry	X	% starting material
1	Cl	40
2	OAc	88
3	PO ₄ H ₂	89
4	PhCO ₂	92
5	BF ₄	>97

In order to test whether the ammonium chloride is destroying the product, a test reaction was performed where ammonium chloride was added to a Davis-type *N*-sulfinyl ketimine that was prepared in lab via the Ellman method (Entry 1, Table 2.2). Because the HPLC column is slightly acidic, the free base imine and hydrolyzed ketone were observed and

measured to indicate loss of starting material. After stirring overnight at room temperature, over half of the starting material was destroyed. After much consideration on how to actively remove ammonium chloride from the reaction, it was decided that instead of attempting to remove the salt byproduct, other ammonium salts should be investigated for how easily they destroy *N*-sulfinyl imine. Chloride was the worst perpetrator. This trend was thought to be due to either the acidity of the corresponding acid: HCl (pKa -7), or to the nucleophilicity of the chloride anion. Other ammonium salts explored were milder and had less nucleophilic counterions. Although the results of ammonium tetrafluoroborate were the most promising (Entry 5) had the most promising results, the other ammonium salts also had a significantly reduced effect on the *N*-sulfinyl ketimine than ammonium chloride and weren't ruled out.

2.2.5 Counterion Screen

Once it was determined that most ammonium salts were less reactive towards *N*-sulfinyl ketimines than ammonium chloride, a counterion screen was performed. Eight benzophenone ketiminium salts were generated using the method in Table 2.1. The acids chosen were based on what was available in the lab. The ketiminium salts then underwent

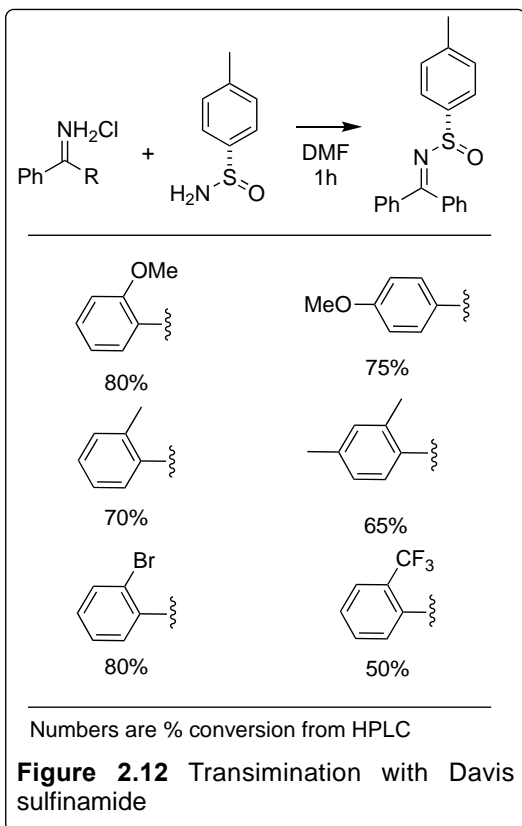
Table 2.3 Counterion Screen

Entry	X	Salt	Comments
1	Salicylic Acid		35% conv.
2	Fluoroboric Acid		95% conv.
3	Benzenesulfonic Acid		85% conv.
4	Oxalic Acid		low solubility in DMF
5	Phosphoric Acid		salt too hygroscopic
6	Benzoic Acid		salt did not crystallize
7	Picolinic Acid		salt did not crystallize
8	Mandelic Acid		low conv. significant byproducts

transimination with Davis sulfinamide. *p*-Toluene sulfinamide was chosen not only to stay consistent with the ammonium salt assay, but also because Davis-type *N*-sulfinyl ketimine formation occurs much faster than Ellman-type and doesn't require heating so the reactions could be run and monitored at ambient temperature. The results of the counterion screen are summarized in Table 2.3. Some salts did not crystallize making isolation of the iminium salt impossible (Entries 6 and 7). As a result, the reaction could not be performed on those substrates. The phosphoric acid iminium salt was extremely hygroscopic and quickly decomposed due to water hydrolysis (Entry 5). Due to the high reactivity with water, this salt was not a viable choice. Of the eight salts tested, the benzenesulfonic acid salt and tetrafluoroboric acid salt performed best (Entries 2 and 3). This result was not surprising considering how well ammonium tetrafluoroborate did in the ammonium salt assay (see Table 2.2). Although benzenesulfonic acid performed well in the screen, tetrafluoroboric acid was chosen for future study based on its consistently good results in the assays and the generally high crystallinity of the iminium salts with this counterion.

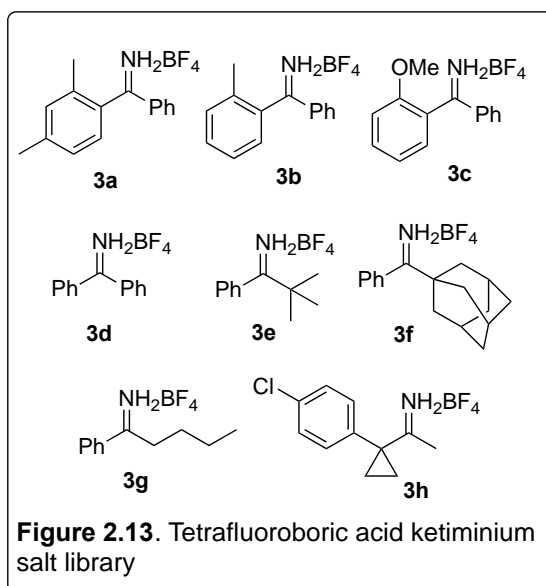
2.2.6 Davis Sulfinamide Screen

While the new library of HBF₄ ketiminium salts was being assembled, formation of the Davis-type *N*-sulfinyl ketimines via HCl ketiminium salts was investigated. Because these reactions occur rapidly at room temperature, it was thought that perhaps the ammonium chloride would have neither the time nor energy required to react with the product. The reactions were worked up after only one hour (versus overnight for reactions with Ellman



sulfinamide). For this substrate scope, only the benzophenone imine-derived salts were examined (Fig. 2.12). After one hour, the reaction seemed to be proceeding rapidly based on the percent conversion monitored by HPLC. One interesting observation was made with the CF₃-substituted benzophenone imine substrate. The reaction conversion was only 50% after one hour. Because the trifluoromethyl group is highly electron withdrawing, one would think the imine carbon would be activated for nucleophilic addition, and the reaction would occur easily.

The question remained: why did the most activated iminium salt have the lowest conversion? When the reaction was run a second time and monitored every ten minutes, it was found that the reaction occurred so rapidly that after an hour, ammonium chloride was already destroying the product at room temperature. Therefore, the most activated substrates cannot avoid the ammonium chloride addition when the hydrochloric acid salt is used. For the rest of the substrates, the reactions were stopped after one hour, worked up, and purified. Despite the overall good conversions, the isolated yields were quite low: ranging from 10-20%. Once the tetrafluoroboric acid ketiminium salt library was complete however, attempting transimination reactions with the hydrochloric acid salts were abandoned. The focus turned instead to a substrate scope with the new starting materials (Fig. 2.13).

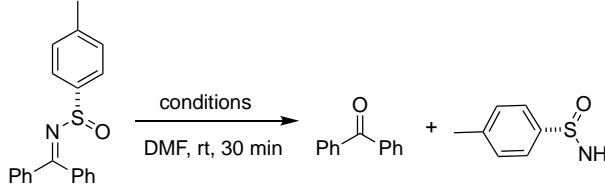


2.2.7 Water Effects in Transimination

With the new ketiminium salts in hand, transiminations with both the Ellman and Davis sulfinamide were performed. As described earlier, reactions with *tert*-butanesulfinamide were run at 80 °C and reactions with *p*-toluenesulfinamide ran at room temperature. Once again, percent conversions were high (observed via HPLC) yet isolated yields were low. The question remained: why don't the reaction conversions correlate to the isolated yields? One consideration is the work up. Because the reaction runs in DMF, the first work up involved diluting the reaction in EtOAc, and quenching it with aqueous ammonium chloride. Once the ammonium chloride problem was discovered, the work up switched to quenching with deionized water (dl water). If the reaction is not complete before work up, the remaining starting material hydrolyzes to the corresponding ketone in the aqueous work up. Therefore, the next factor to investigate was whether the product can also be hydrolyzed in the work up, which would explain inconsistency in reaction conversion and yield. Once again, the Davis-type benzophenone *N*-sulfinyl ketimine was used as a sample substrate. The product was dissolved in DMF at room temperature,

stirred for 30 min, then monitored via HPLC (Table 2.4). When using reagent grade DMF that is marketed as anhydrous, 6% hydrolysis of product was observed after 30 min (Entry 1). A sample of the DMF was run through Karl Fischer titration to determine the water content.²⁸ Although the DMF purchased was supposed to be anhydrous, it contained 500 ppm of water. That trace amount of water was able to hydrolyze 6% of the desired product in only 30 min. If a reaction is allowed to run for multiple hours, both the starting material and product will be hydrolyzed due to solvent's water content. Worse still,

Table 2.4 Product hydrolysis rates in various conditions

		
Entry	Conditions	% Hydrolysis
1	"anhydrous" DMF 500 ppm H ₂ O	6
2	5% H ₂ O in DMF	26
3	5% NH ₄ Cl _(aq) in DMF	39

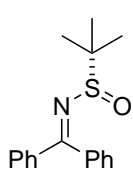
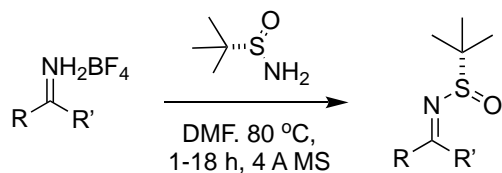
when DMF was doped with 5% water, a quarter of the product hydrolyzes in 30 min (Entry 2). Not surprisingly, aqueous ammonium chloride was the worst offender destroying nearly 40% of the product in 30 min (Entry 3). Therefore, even when the work up was switched to dl water with the first round of substrates (HCl iminium salts), the product was essentially being washed with aqueous ammonium chloride anyway. These results would explain why the test reactions in Figure 2.12 failed.

2.2.8 Optimal Conditions for Transimination and Substrate Scope

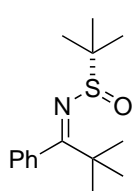
It was established that ammonium chloride and water are the major factors causing the transiminations to fail. Therefore, the optimal reaction conditions were implemented. First, as mentioned earlier, the iminium salts were switched from the hydrochloric acid salts to the tetrafluoroboric acid salts to prevent any product destruction due to byproduct reactions. The reaction conditions had to also be truly anhydrous. Therefore, transiminations were attempted with both the Ellman and Davis type sulfinamide under the optimal conditions. Each reaction was run on a 1.0 g scale in 5.0 mL DMF. The stock DMF was dried with activated molecular sieves, and the water content was measured via Karl Fischer titration. The new DMF water content was 13 ppm, significantly less than what was used previously. Crushed activated molecular sieves were also added to each reaction prior to sulfinamide addition. This protocol was performed to try to eliminate any water that might have been absorbed by the ketiminium salts. As before, reactions with Davis sulfinamide were run at room temperature with 1.2 equivalents of the sulfinamide. Because the Ellman sulfinamide reactions required much more heat to turnover, it was found that starting with 2 equivalents of the sulfinamide helped reaction rates, and adding more equivalents over time allowed the reaction to reach higher percent conversions. This trend was thought to be due to the Ellman sulfinamide degrading over time at such a high temperature. Once the reaction was complete or the highest reaction conversion was observed, the reaction was diluted with EtOAc as before, and quickly washed with aqueous sodium bicarbonate to try to prevent any acid-mediated hydrolysis of the desired *N*-sulfinyl ketimine product.

Due to time constraints, a limited substrate scope was performed (Fig. 2.14). Because transimination with the Ellman sulfinamide was more time-consuming and involved, only four substrates were completed (Fig. 2.14a). These four compounds however, exhibit the

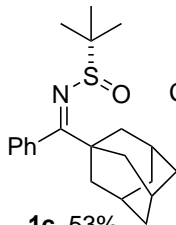
a.



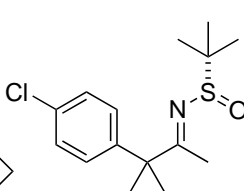
1a, 71%*



1b, 75%



1c, 53%

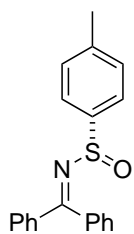
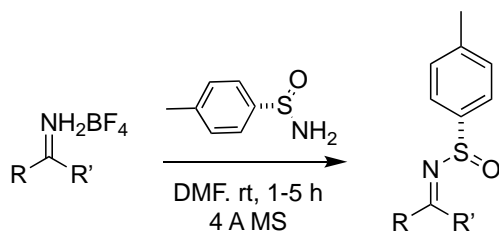


1d, 63%

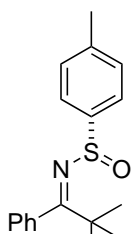
Isolated yields of purified products

*98.4% ee by chiral column

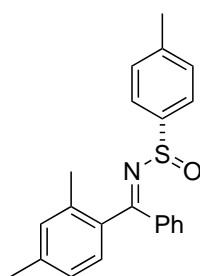
b.



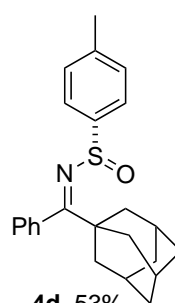
4a, 69%



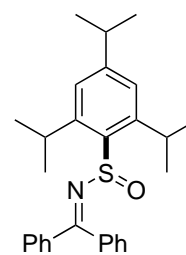
4b, 86%



4c, 76%



4d, 53%



5a, 58%*

Isolated yields of purified product

*Reaction run at 80 °C using (*R*)-TIPPS

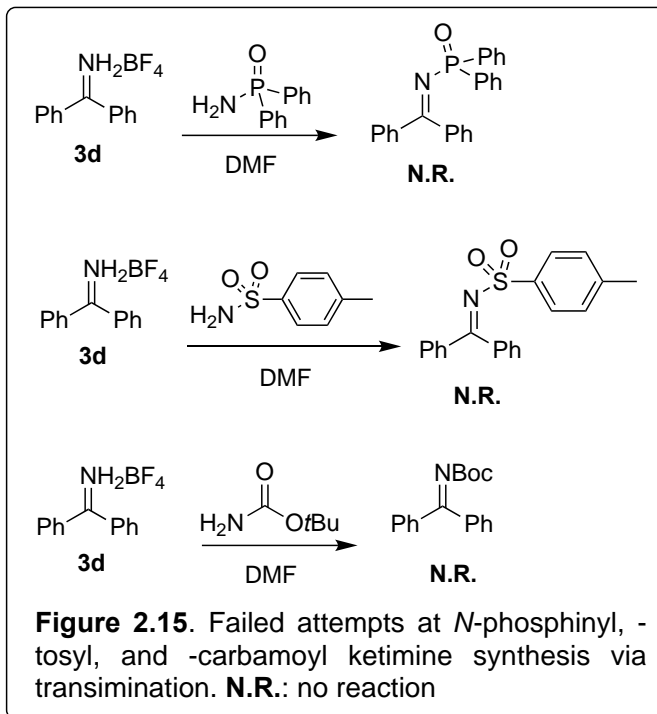
Figure 2.14. Preliminary results for transimination reactions between ketiminium salts and **a.** *tert*-butane sulfinamide and **b.** *p*-toluene sulfinamide

success of the reaction for different types of ketimines. Benzophenone imine 1a showed that not only does the reaction work on doubly aromatic ketimines, but also that there is essentially no epimerization (98.4% enantiomeric excess by chiral column). For ketimine 1b and 1c, the reaction worked despite the sterically bulky *t*-butyl and adamantyl substituents. What is interesting about 1d is that the reaction worked on a substrate that has two alkyl substituents, which was thought to be more difficult due to electronic effects. It is also important to note that the numbers reported are isolated yields that were not as high as the reaction conversion, but were much higher than was observed by the previous reaction methods.

In transimination reactions involving the Davis sulfinamide, once again the benzophenone imine ketimine was generated in a moderate yield (4a, Fig. 2.14b). Substrates with sterically bulky groups were attempted and worked with ranging degrees of success. As before, the *t*-butyl substituent (4b) had an excellent yield. Ketimine 4c is a benzophenone imine-type substrate with a 2,4-dimethyl substitution that had a moderate yield. Surprisingly, 4d with a large adamantyl group was also generated, albeit with a modest yield of 53%. Another steric effect to consider is on the sulfinyl group. Therefore, another transimination reaction was performed on the benzophenone iminium salt with (*R*)-triisopropylphenyl sulfinamide (TIPPS). The synthesis and use of (*R*)-TIPPS was developed in order to fine-tune stereoselectivity when the Ellman and Davis sulfinamide failed.^{29,30} The yield for 5a was modest and required heating similar to the Ellman sulfinamide transimination reactions. Although the yields range from excellent to moderate, this is the first reported synthesis of *N*-sulfinyl ketimines that does not require Ti(OEt)₄ or any other Lewis acid additives.

2.2.9 Synthesis of *N*-Phosphinyl, -Tosyl, and -Carbamoyl Ketimines via Transimination

Using the same conditions outlined in section 2.2.8, the synthesis of *N*-phosphinyl, -tosyl, and -carbamoyl ketimines was attempted with the corresponding phosphinamide, sulfonamide, and carbamate, respectively (Fig. 2.15). Unfortunately, in all three cases, no product was observed. It is unclear why the reaction only worked for sulfinamides and should be investigated further. These reactions were attempted at room temperature



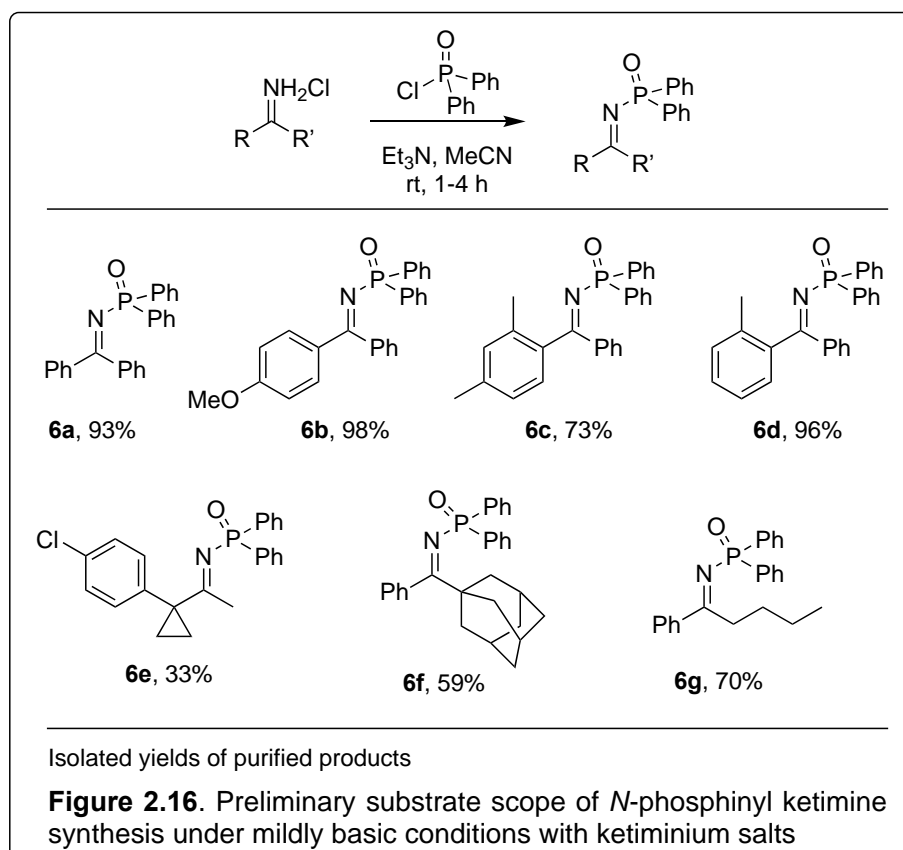
and monitored via HPLC. Perhaps with more fine-tuning of the reaction conditions product would be able to form, but due to time restrictions, another method was investigated.

2.2.10 Mildly Basic Method of Generating *N*-Phosphinyl and -Tosyl Ketimines

2.2.10.1 *N*-Phosphinyl Ketimines

As mentioned, the HCl ketiminium salts could not be used for transimination due to the ammonium chloride byproduct. Because they were still available in the lab, the HCl ketiminium salts were chosen as test substrates for a novel reaction to generate the

various substituted imines. It was hypothesized that the acidic iminium proton could be deprotonated upon treatment with a mild base. This would in turn create a nucleophilic imine that could attack a good electrophile such as an anhydride or acyl chloride. Therefore, instead of using a phosphinamide or sulfonamide as the nucleophile that would attack the electrophilic ketiminium salt, the imine could act as a nucleophile to a corresponding electrophile. At room temperature, the HCl ketiminium salts were dissolved in 2.5 equivalents of Et₃N and seven volumes of acetonitrile. Diphenylphosphinic chloride (1.2 equivalents) was added and the reactions were monitored via HPLC. Most reactions were completed in one hour with some reactions taking as long as four hours. The products were easily purified via column chromatography to generate *N*-phosphinyl ketimines in good to excellent yields (Fig. 2.16). The benzophenone imine-derived substrates worked best with electron donating groups producing the highest yield (6b).

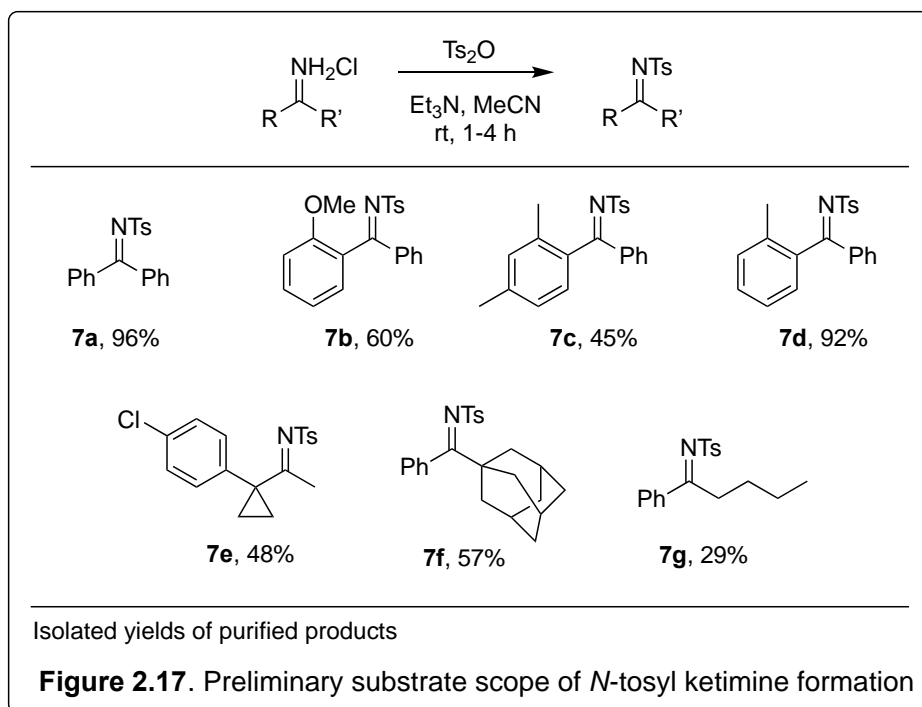


Because the reactions are under basic conditions, the enolizable substrates (6e and 6g) had lower yields. Although 6e had the poorest result, it was surprising to see any product at all on the doubly alkyl-substituted substrate. This method is also much simpler and milder than those outlined in Figure 2.5 for *N*-phosphinyl ketimines. The atom economy of these reactions is also favorable for process chemistry with an average of 84%.

2.2.10.2 *N*-Tosyl Ketimines

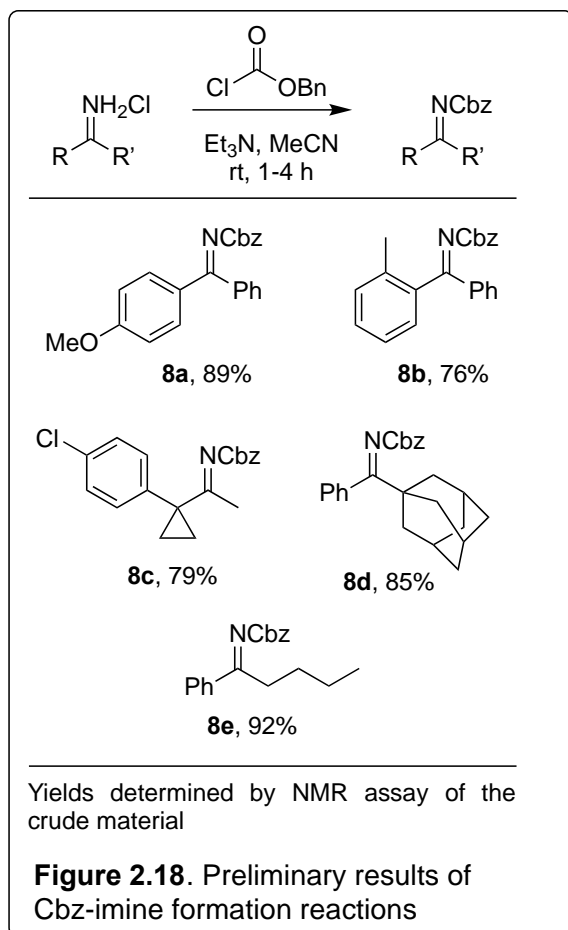
Using the same conditions for *N*-phosphinyl ketimines, the corresponding *N*-tosyl ketimines were generated using *p*-toluenesulfonic anhydride as the electrophile (Fig. 2.17). The yields were consistent with the phosphinyl imines for the most part with some differences. The doubly alkylated ketimine 7e had a slightly better yield for the tosyl imine. The other enolizable substrate 7g had a significantly lower yield compared to the phosphinyl imine (70% and 29%, respectively). As expected, the benzophenone imine-derived substrates reacted better than the alkyl-containing salts. Once again, this new method is less time-consuming and milder than previously reported methods (see Fig. 2.6). It is also much more process-friendly with little concerns in scalability. Although the concentration of the reaction and equivalents may need to be optimized for large-scale reactors, these reactions require no tedious work up such as filtering titanium byproduct, and purification is trivial. That these reactions are complete in a short period of time and are performed at room temperature is an added bonus. The atom economy for this reaction is not as favorable as the *N*-phosphinyl ketimine reaction due to the nature of

tosyl anhydride being pseudo-two equivalents of tosyl. Unlike the previous methods however, this new reaction does not require heat, additives, or any type of catalysts.



2.2.10.3 *N*-Carbamoyl Ketimines

As mentioned earlier, *N*-carbamoyl ketimines are synthetically useful intermediates but can be difficult to generate in an efficient manner (see Fig. 2.7). Therefore, the new mildly basic method with ketiminium salts was attempted with benzyl chloroformate to produce Cbz-protected ketimines (Fig. 2.18). As before, the limited substrate scope performed focused on aromatic versus alkyl substituents and sterically small versus bulky groups. Although product was observed via HPLC and NMR, Cbz-protected imines are not stable to column chromatography on silica gel. When one sample was subjected to purification via column chromatography, no product was isolated, and the corresponding ketone was recovered. Therefore, the yields noted in Figure 2.18 are determined by NMR assay of



the crude material. This minor drawback can be overcome by performing the next reaction on the crude material. The crude NMR had very few impurities as the minor excess of benzyl chloroformate is removed upon work up of the reaction. Another solution would be to recrystallize the product. It is suspected that the product could be a solid despite the crude material being an oil. The state of the crude could be due to hydrolyzed unreacted starting material, which would be the corresponding ketone and most likely an oil. Due to time restrictions, these solutions could not be investigated. It should be noted that in

the methods described in Figure 2.7, purification was typically not performed either. Regardless of the purification obstacles, this is the first reported method of generating Cbz-protected ketimines using ketiminium salts under mildly basic conditions.

2.2.11 Conclusions

A library of *N*-sulfinyl ketimines was generated through a novel use of transimination with ketiminium salts and chiral sulfinamides under optimal conditions. This method is much more process chemistry-oriented due to the cheap starting materials, ease of generating the ketiminium salts, and elimination of the titanium reagent requirement. These reactions

also have good atom economy, with an average of 73% for the Ellman-type sulfinimines and 75% for the Davis-type. Despite the many obstacles that had to be overcome for the reaction to work, this is the first reported successful, Lewis acid and titanium-free synthesis of *N*-sulfinyl ketimines via transimination.

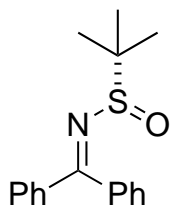
Although transimination was not successful with phosphinamides or sulfonamides yet, a new method was developed by switching the roles of nucleophile and electrophile in the reaction under basic conditions. *N*-tosyl, -phosphinyl, and -carbamoyl ketmines were produced with varying degrees of success. This method is also process-friendly as the reactions do not require heat, catalysts, or unstable intermediates. The starting materials and reagents are also cheap, stable, and easy to make. These methods show great promise in developing *N*-substituted ketimines for the synthesis of pharmaceutically interesting compounds.

2.3 EXPERIMENTAL

General experimental. All reactions, unless specified, were conducted under an atmosphere of N₂. Where appropriate, control of temperature was achieved with a solid CO₂/acetone bath, an ice-bath, or a heated oil bath. All commercially available reagents were purchased from Sigma-Aldrich.

¹H NMR spectra were recorded at 400 MHz and/or at 500 MHz and calibrated to the residual CHCl₃ peak at 7.26 ppm. The following abbreviations are used for peak multiplicities: br s (broad singlet), s (singlet); d (doublet); t (triplet); q (quartet); quintet (quin); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets). ¹³C NMR spectra were recorded at 100MHz and/or at 125 MHz and calibrated to the CDCl peak at 77.23 ppm. Chemical shifts are reported in units of parts per million (ppm). Coupling constants, *J*, are reported in Hertz (Hz). Flash chromatography was performed on Combi-Flash Rf+ automated system with silica columns at Boehringer Ingelheim in Danbury, Connecticut.

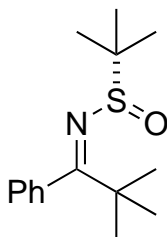
General procedure for transimination with (S)-tert-butanesulfinamide using 1a as example:



(S)-N-(Diphenylmethylene)-2-methylpropane-2-sulfinamide (1a)

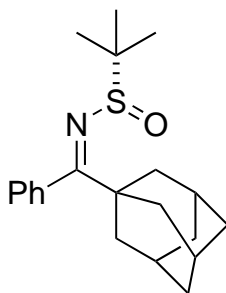
(Diphenyl)methaniminium tetrafluoroborate (**3d**) (1.00 g, 3.72 mmol) and (S)-tert-butanesulfinamide (0.902 g, 7.44 mmol) were combined in DMF (5.0 mL) and stirred at rt for 15 h with 1 eq. of (S)-TBSA added every two hours for the first six hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with aqueous NaHCO₃ (25 mL). The organic phase was dried with Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by silica column chromatography using 10% MTBE/hexane as eluent afforded (S)-N-(diphenylmethylene)-2-methylpropane-2-sulfinamide **1a** (0.754 g, 71% yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.83–7.18 (m, 10H), 1.20 (s, 9H).³¹

Note: Modifications (if any) on the above general procedure are detailed in the following reactions.



(S)-N-(2,2-Dimethyl-1-phenylpropylidene)-2-methylpropane-2-sulfinamide (1b)

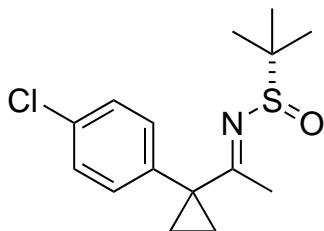
According to the general procedure, using 2,2-dimethyl-1-phenylpropan-1-iminium tetrafluoroborate (**3e**) (1.00 g, 4.02 mmol), (S)-TBSA (0.973 g, 8.03 mmol), and DMF (5.0 mL) stirred for 1 h at 80 °C, followed by purification by chromatography on SiO₂ (10% MTBE/hexanes) provided (S)-N-(2,2-dimethyl-1-phenylpropylidene)-2-methylpropane-2-sulfinamide (0.800 g, 75% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.53–7.32 (m, 3H), 7.18–7.03 (m, 2H), 1.17 (s, 9H), 1.10 (s, 9H).³¹



(S)-N-(Adamantyl-1-phenylmethylene)-2-methylpropane-2-sulfinamide (1c)

According to the general procedure, using adamantyl(phenyl)methaniminium tetrafluoroborate **3f** (1.00 g, 3.06 mmol), (S)-TBSA (1.48 g, 12.2 mmol), and DMF (5.0 mL) stirred for 1 h at 80 °C, followed by purification by chromatography on SiO₂ (10% MTBE/hexanes) provided (S)-N-(adamantyl-1-phenylmethylene)-2-methylpropane-2-sulfinamide (0.410 g, 39% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.36 (m,

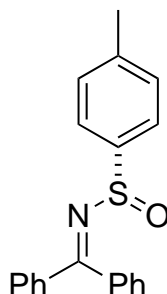
3H), 7.03 (br, 2H), 2.02 (m, 3H), 1.84 (m, 6H), 1.68 (d, $J = 12.6$ Hz, 3H), 1.66 (d, $J = 12.6$ Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.1, 136.4, 128.2, 127.6, 126.5, 44.3, 39.5, 36.3, 28.1, 22.1.



(S)-N-(1-(4-Chlorophenyl)cyclopropyl)ethylidene-2-methylpropane-2-sulfinamide (1d)

According to the general procedure, using (1-(4-chlorophenyl)cyclopropyl)ethaniminium tetrafluoroborate **3h** (1.00 g, 4.34 mmol), (S)-TBSA (2.10 g, 17.4 mmol), and DMF (5.0 mL) stirred for 2 h at 80 °C, followed by purification by chromatography on SiO_2 (10% MTBE/hexanes) provided (S)-N-(1-(4-chlorophenyl)cyclopropyl)ethylidene-2-methylpropane-2-sulfinamide (0.759 g, 63% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.27 (m, 4H), 2.17 (s, 3H), 1.61 (m, 1H), 1.54 (m, 1H), 1.18 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 186.4, 139.7, 133.0, 131.7, 128.5, 56.4, 35.7, 22.0, 21.5, 17.2, 17.0.

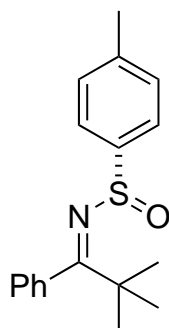
General procedure for transimination with (S)-p-toluenesulfinamide using 4a as example:



(S)-N-(Diphenylmethylene)-4-toluenesulfinamide (4a)

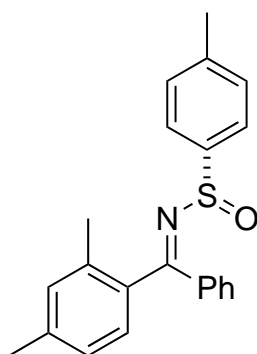
(Diphenyl)methaniminium tetrafluoroborate (**3d**) (1.00 g, 3.72 mmol) and (S)-p-toluenesulfinamide (0.692 g, 4.46 mmol) were combined in DMF (5.0 mL) and stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with aqueous NaHCO₃ (25 mL). The organic phase was dried with Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by SiO₂ column chromatography using 10% MTBE/hexane as eluent afforded (S)-N-(diphenylmethylene)-4-toluenesulfinamide **4a** (0.820 g, 69% yield) as white solid. ¹H NMR (500 MHz) δ 7.88 (d, *J* = 7.6 Hz, 2 H), 7.72 (d, *J* = 8.2 Hz, 2 H), 7.47 (t, *J* = 6.7 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 2.78 (s, 3 H).¹⁵

Note: Modifications (if any) on the above general procedure are detailed in the following reactions.



(S)-N-(2,2-Dimethyl-1-phenylpropylidene)-4-toluenesulfinamide (4b)

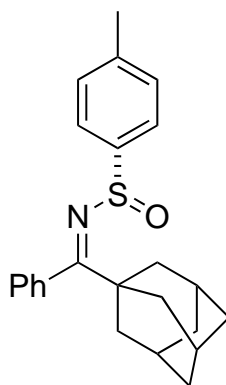
According to the general procedure, 2,2-Dimethyl-1-phenylpropan-1-iminium tetrafluoroborate **3e** (1.00 g, 4.02 mmol), (S)-*p*-toluenesulfinamide (0.748 g, 4.82 mmol), and DMF (5.0 mL) stirred at rt for 15 h followed by purification by chromatography on SiO₂ (10% MTBE/hexane) provided (S)-N-(2,2-dimethyl-1-phenylpropylidene)-4-toluenesulfinamide (1.04 g, 86% yield) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.47 (m, 2H), 7.40-7.39 (m, 3H), 7.26-7.24 (m, 2H), 6.95 (br s, 2H), 2.39 (s, 3H), 1.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 188.9, 143.8, 142.2, 137.1, 129.7, 128.7, 128.1, 126.1, 125.5, 42.0, 27.9, 21.6.



(S)-N-(2,4-Dimethylphenyl(phenyl)methylene)-4-toluenesulfinamide (4c)

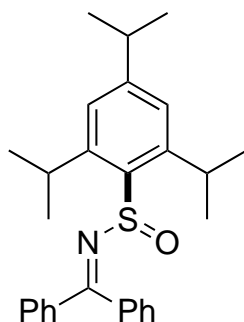
According to the general procedure, (2,4-dimethylphenyl)(phenyl)methaniminium tetrafluoroborate **3a** (1.00 g, 3.53 mmol), (S)-*p*-toluenesulfinamide (0.658 g, 4.24 mmol), and DMF (5.0 mL) stirred at rt for 15 h followed by purification by chromatography on SiO₂

(10% MTBE/hexane) provided (*S*)-*N*-(2,4-dimethylphenyl(phenyl)methylene)-4-toluenesulfonamide (0.891 g, 76% yield) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, J = 7.4 Hz, 2H), 7.49 (d, J = 7.9 Hz), 7.44 (m, 1H), 7.32 (m, 2H), 7.27 (d, J 7.6 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 2.36 (s, 3H), 2.25 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.8, 143.4, 142.4, 136.4, 135.9, 134.1, 134.1, 132.6, 129.6, 129.2, 128.6, 127.7, 127.3, 125.6, 21.5, 20.0, 19.4.



(*S*)-*N*-(Adamantyl-1-phenylmethylene)-4-toluenesulfonamide (4d)

According to the general procedure, using adamantyl(phenyl)methaniminium tetrafluoroborate **3f** (1.00 g, 3.06 mmol), (*S*)-*p*-toluenesulfonamide (0.570 g, 3.67 mmol), and DMF (5.0 mL) stirred for 4 h, followed by purification by chromatography on SiO_2 (10% MTBE/hexanes) provided (*S*)-*N*-(adamantyl-1-phenylmethylene)-4-toluenesulfonamide (0.695 g, 53% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, J = 8.2 Hz, 2H), 7.40 (m, 3H), 7.25 (d, J = 8.2 Hz, 2H), 6.92 (br, 2H), 2.40 (s, 3H), 2.00 (m, 3H), 1.82 (m, 6H), 1.67 (d, J = 12.6 Hz, 3H), 1.64 (d, J = 12.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.1, 143.5, 141.7, 136.1, 129.3, 128.3, 127.6, 125.8, 125.0, 43.3, 38.9, 35.9, 27.7, 27.7, 21.2.



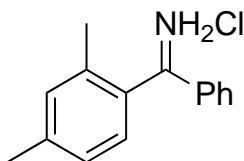
(R)-N-(Diphenylmethylene)-2,4,6-triisopropylphenyl-2-sulfonamide (5a)

According to the general procedure, using (diphenyl)methaniminium tetrafluoroborate **3d** (1.00 g, 3.74 mmol), (*R*)-2,4,6-triisopropylphenylsulfonamide (1.20 g, 4.49 mmol), and DMF (5.0 mL) stirred for 4 h at 80 °C, followed by purification by chromatography on SiO₂ (10% MTBE/hexanes) provided (*S*)-*N*-(diphenylmethylene)-2,4,6-triisopropylphenyl-2-sulfonamide (0.936 g, 58% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.00-6.80 (m, 10H), 7.02 (s, 2H), 3.81 (br, 2H), 2.91-2.81 (m, 1H), 1.24-1.21 (m, 12H), 1.18-1.16 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 152.7, 150.0, 138.6, 137.2, 128.3, 122.6, 34.4, 28.8, 25.4, 23.8, 23.8.

General Procedure for Synthesis of N-H Imine Hydrochloride Salts (2)

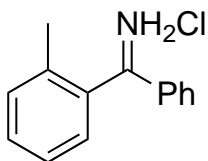
A round-bottom flask was charged with nitrile (5.00 g, 1 eq.) and THF (1 M). The mixture was cooled to -78 °C and PhLi (1.1 eq., 1.8 M in di-*n*-butyl ether) was added dropwise over 0.5 h. After addition, the resulting mixture was stirred for 2 h and quenched with anhydrous MeOH (10 mL). The mixture was then stirred at rt for 2 h. The suspension was filtered through celite, and the filtrate was concentrated under vacuum. The residue was dissolved in MTBE (1 M) and treated with HCl/Et₂O (1.1 eq., 1 M). The slurry was stirred for 30 min and filtered to obtain the product as free-flowing off-white to yellow solids.^{27,32}

Note: Modifications (if any) on the above general procedure are detailed in the following reactions.



(2,4-Dimethylphenyl)(phenyl)methaniminium chloride (2a)

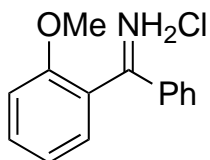
According to the general procedure, 2,4-dimethylbenzonitrile (5.00 g, 38.1 mmol) and PhLi (23.3 mL) were combined in THF (38 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (38 mL) and treated with HCl/Et₂O (34.7 mL). The filtered solid was off-white. ¹H NMR (MeOD, 500 MHz) δ 7.90-7.94 (m, 3H), 7.71-7.74 (m, 2H), 7.59 (d, J = 10 Hz, 1H), 7.43 (m, 1H), 7.37 (d, J = 10 Hz, 1H), 2.41 (s, 6H).



Phenyl(o-tolyl)methaniminium chloride (2b)

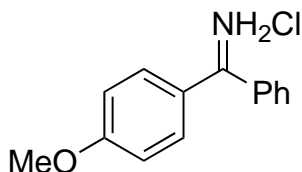
According to the general procedure, *o*-tolubenzonitrile (5.00 g, 42.7 mmol) and PhLi (26.1 mL) were combined in THF (43 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (43 mL) and treated with HCl/Et₂O (47.0 mL). The filtered solid was off-white. ¹H NMR (DMSO-d₆, 400

MHz) δ 13.45 (br s, 2H), 7.89 (d, J = 7.2 Hz, 2H), 7.83 (t, J = 7.2 Hz, 1H), 7.65–7.57 (m, 3H), 7.47–7.40 (m, 3H), 2.12 (s, 3H).



(2-Methoxyphenyl)(phenyl)methaniminium chloride (2c)

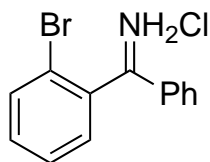
According to the general procedure, 2-methoxybenzonitrile (5.00 g, 37.6 mmol) and PhLi (23.0 mL) were combined in THF (37.6 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (38.0 mL) and treated with HCl/Et₂O (41.3 mL). The filtered product was a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 13.20 (br s, 2H), 7.86 (d, J = 7.6 Hz, 2 H), 7.79 (t, J = 7.6 Hz, 1 H), 7.75–7.70 (m, 1H), 7.61 (m, 2H), 7.45–7.42 (m, 1H), 7.31 (d, J = 8.4 Hz, 1 H), 7.16 (t, J = 7.6 Hz, 1 H), 3.72 (s, 3H).



(4-Methoxyphenyl)(phenyl)methaniminium chloride (2d)

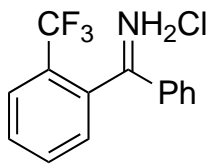
According to the general procedure, 4-methoxybenzonitrile (5.00 g, 37.6 mmol) and PhLi (23.0 mL) were combined in THF (37.6 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (38.0 mL) and treated with HCl/Et₂O (41.3 mL). The filtered product was a yellow solid. ¹H NMR

(DMSO-*d*₆, 400 MHz) δ 13.20 (br s, 2H), 7.86 (d, J = 7.6 Hz, 2 H), 7.79 (t, J = 7.6 Hz, 1 H), 7.73 (m, 1H), 7.61 (m, 2H), 7.44 (m, 1H), 7.31 (d, J = 8.4 Hz, 1 H), 7.16 (t, J = 7.6 Hz, 1 H), 3.72 (s, 3H).



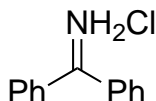
(2-Bromophenyl)(phenyl)methaniminium chloride (2e)

According to the general procedure, 2-bromobenzonitrile (5.00 g, 27.5 mmol) and PhLi (16.8 mL) were combined in THF (27.5 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (27.5 mL) and treated with HCl/Et₂O (30.2 mL). The filtered product was a yellow solid. ¹H NMR (MeOD, 500 MHz) δ 7.90-7.93 (m, 2H), 7.83 (m, 2H), 7.67-7.73 (m, 5H).



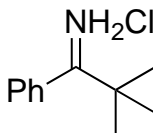
Phenyl(2-(trifluoromethyl)phenyl)methaniminium chloride (2f)

According to the general procedure, 2-(trifluoromethyl)benzonitrile (5.00 g, 29.2 mmol) and PhLi (17.9 mL) were combined in THF (29.2 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (29.2 mL) and treated with HCl/Et₂O (32.1 mL). The filtered product was a yellow solid. ¹H NMR (MeOD, 500 MHz) δ 8.05-8.06 (m, 1H), 7.95-8.00 (m, 2H), 7.90-7.93 (m, 1H), 7.78-7.81 (m, 3H), 7.68-7.71 (m, 2H).



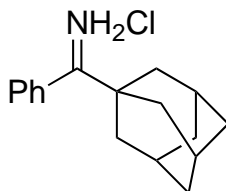
(Diphenyl)methaniminium chloride (2g)

Commercially available benzophenone imine (5.00 g, 27.5 mmol) was dissolved in MTBE (27.5 mL) and treated with HCl/Et₂O (30.4 mL). The filtered product was a white solid. ¹H NMR (MeOD, 400 MHz) δ 7.62-7.48 (m, 6H), 7.67-7.88 (m, 4H).



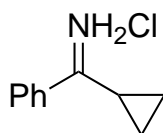
2,2-Dimethyl-1-phenylpropan-1-iminium chloride (2h)

According to the general procedure, trimethylacetonitrile (5.00 g, 60.2 mmol) and PhLi (36.8 mL) were combined in THF (60.2 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (60.2 mL) and treated with HCl/Et₂O (66.2 mL). The filtered product was a tan solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 12.74 (br s, 2H), 7.66-7.61 (m, 1H), 7.56-7.55 (m, 4H), 1.33 (s, 9H).



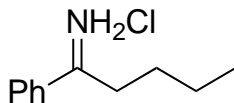
Adamantyl(phenyl)methaniminium chloride (2i)

According to the general procedure, 1-adamantanecarbonitrile (3.00 g, 18.6 mmol) and PhLi (11.4 mL) were combined in THF (18.6 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (18.6 mL) and treated with HCl/Et₂O (20.5 mL). The filtered product was a tan solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.55–7.13 (m, 5H), 2.03 (m, 5H), 1.85 (m, 4H), 1.68 (m, 6H).³³



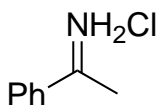
Cyclopropyl(phenyl)methaniminium chloride (2j)

Cyclopropanecarbonitrile (3.00 g, 45.0 mmol) in diethyl ether (3.0 mL) was added dropwise to PhLi (27.5 mL, 1.8 M in di-*n*-butyl ether) over a 5 min period, and when the exothermic reaction had ceased the brown solution was allowed to stir an additional 1 h. The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (45.0 mL) and treated with HCl/Et₂O (49.5 mL). The filtered product was a white powder. ¹H NMR (MeOD, 400 MHz) δ 7.77 (m, 5 H), 2.05 (quin, *J* = 7.0 Hz, 1H), 0.94 (d, *J* = 7.0 Hz, 4H).³⁴



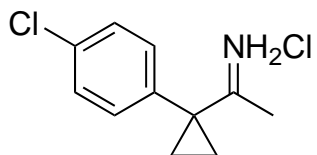
1-Phenylpentan-1-iminium chloride (2k)

According to the general procedure, benzonitrile (5.00 g, 48.5 mmol) and n-butyllithium (21.3 mL, 2.5 M in hexanes) were combined in THF (48.5 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (53.3 mL) and treated with HCl/Et₂O (53.3 mL). The filtered product was a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 12.77 (br s, 2H), 8.12–8.10 (m, 2H), 7.85–7.81 (m, 1H), 7.70–7.66 (m, 2H), 3.24 (t, *J* = 7.6 Hz, 2 H), 1.61–1.53 (m, 2H), 1.40–1.31 (m, 2H), 0.89 (t, *J* = 7.6 Hz, 3 H).



1-Phenylethan-1-iminium chloride (2l)

According to the general procedure, benzonitrile (5.00 g, 48.5 mmol) and MeLi (33.4 mL, 1.6 M in diethyl ether) were combined in THF (48.5 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (48.5 mL) and treated with HCl/Et₂O (53.3 mL). The filtered product was a white solid. ¹H NMR (MeOD, 400 MHz) 8.07–8.04 (m, 2H), 7.86–7.82 (m, 2H), 7.70–7.65 (m, 2H), 2.91 (s, 3H).



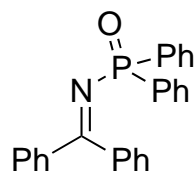
(1-(4-Chlorophenyl)cyclopropyl)ethaniminium chloride (2n)

According to the general procedure, the nitrile (5.00 g, 31.8 mmol) and MeLi (21.9 mL, 1.6 M in diethyl ether) were combined in THF (31.8 mL). The reaction was quenched with MeOH, filtered through celite, and concentrated. The crude material was dissolved in MTBE (31.8 mL) and treated with HCl/Et₂O (35.0 mL). The filtered product was a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 7.55 (br, 2H), 7.36 (s, 4H), 1.90 (s, 3H), 1.47 (dd, *J* = 4.0, 7.1 Hz, 2H), 1.12 (dd, *J* = 4.0, 7.1 Hz, 2H); ¹³C NMR (DMSO-d₆, 100 MHz) δ 207.2, 140.1, 132.9, 132.3, 128.8, 37.1, 28.4, 18.0.

General Procedure for Synthesis of N-H Imine Tetrafluoroboric Salts (3)

The procedure for compounds 3a-3h is identical to the procedure for the N-H imine hydrochloride salts (2) with the following changes: Upon formation of the imine, the crude material was dissolved in MTBE and treated with tetrafluoroboric acid diethyl ether complex (1.1 eq.) to produce the N-H imine tetrafluoroboric salts (3).

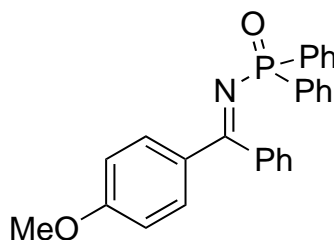
*General procedure for phosphinic and tosyl imine formation using **6a** as example:*



***N*-((Diphenyl)methylene)-*P,P*-diphenylphosphinic amide (6a)**

(Diphenyl)methanimine HCl **2g** (0.500 g, 2.30 mmol) was dissolved in MeCN (7.5 mL) and. Et₃N (1.59 mL, 11.5 mmol). Diphenylphosphinic chloride (0.653 g, 2.76 mmol) was added and the reaction mixture stirred at rt. After 3 h, the reaction was diluted with CH₂Cl₂ (100 mL) and washed with H₂O (100 mL). The organic phase was dried with Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by silica column chromatography using 35% EtOAc/hexane as eluent afforded phosphinic *N*-((diphenyl)methylene)-*P,P*-diphenylphosphinic amide **6a** (0.816 g, 93% yield) as white solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.92 (ddd, *J* = 11.8, 8.0, 1.4 Hz, 4H), 7.57-7.55 (m, 4H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.45 - 7.36 (m, 10H).³⁵

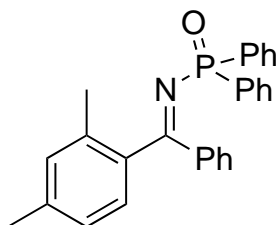
Note: Modifications (if any) on the above general procedure were detailed in the following reactions.



***N*-((4-Methoxyphenyl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide (6b)**

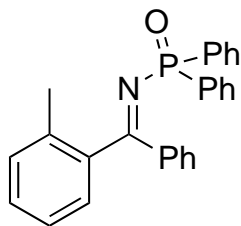
According to the general procedure, (4-methoxyphenyl)(phenyl)methanimine HCl **2d** (0.500 g, 2.02 mmol) and diphenylphosphinic chloride (0.573 g, 2.42 mmol) were

combined in MeCN (7.5 mL) and Et₃N (1.40 mL, 10.1 mmol). After 3 h, the reaction was worked up and purified by column chromatography using 35% EtOAc/hexane as eluent to afford *N*-((4-methoxyphenyl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide **6b** (0.815 g, 98% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (m, 4H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.34 (m, 10H), 7.15 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 181.2 (d, *J* = 7.9 Hz), 162.7, 135.7, 134.4, 132.2, 131.4 (d, *J* = 9.1 Hz), 131.2 (d, *J* = 9.1 Hz), 130.9 (d, *J* = 2.5 Hz), 130.6 (d, *J* = 1.8 Hz), 130.3, 129.5, 128.9, 128.1 (d, *J* = 12.4 Hz), 127.8 (d, *J* = 13.1 Hz), 127.5, 113.2, 55.3;



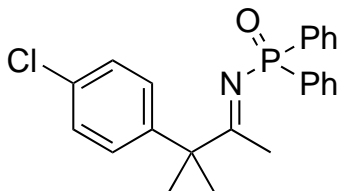
***N*-((2,4-Dimethylphenyl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide (**6c**)**

According to the general procedure, using (2,4-dimethylphenyl)(phenyl)methaniminium chloride **2a** (0.500 g, 2.02 mmol), diphenylphosphinic chloride (0.578 g, 2.44 mmol), and Et₃N (1.4 mL, 10.2 mmol) in MeCN (7.5 mL) stirred for 6 h, followed by purification by chromatography on SiO₂ (35% EtOAc/hexanes) provided *N*-((2,4-dimethylphenyl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide **6c** (0.582 g, 73% yield) as a light orange oil. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (m, 6H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.42 (m, 8H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 2H), 1.88 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 181.9 (d, *J* = 7.4 Hz), 138.2, 137.9, 137.8, 134.9, 133.9, 133.6, 132.8, 131.6 (d, *J* = 8.8), 131.1 (d, *J* = 2.4), 128.7 (d, *J* = 18.5 Hz), 128.4, 128.1, 128.0, 126.9, 19.5;



***N*-((2-Methylphenyl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide (6d)**

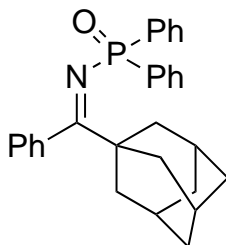
According to the general procedure, using phenyl(*o*-tolyl)methaniminium chloride **2b** (0.500 g, 2.16 mmol), diphenylphosphinic chloride (0.613 g, 2.59 mmol), and Et₃N (1.5 mL, 10.8 mmol) in MeCN (7.5 mL) stirred for 2 h, followed by purification by chromatography on SiO₂ (35% EtOAc/hexanes) provided *N*-((2-methylphenyl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide (0.789 g, 96% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (m, 6H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.42 (m, 8H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.15 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 1.88 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 182.3 (d, *J* = 7.3 Hz), 138.8 (d, *J* = 22.6 Hz), 138.1 (d, *J* = 12.0 Hz), 135.3, 134.3, 134.0, 132.8, 131.6 (d, *J* = 9.0 Hz), 131.2 (d, *J* = 2.5 Hz), 129.7, 129.5, 128.9, 128.5, 128.2, 128.1, 127.1, 125.1, 19.6;



***N*-(1-(4-Chlorophenyl)cyclopropyl)ethylidene)-*P,P*-diphenylphosphinic amide (6e)**

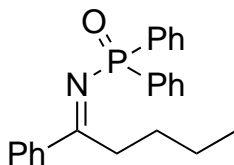
According to the general procedure, using (1-(4-chlorophenyl)cyclopropyl)ethaniminium chloride **2n** (0.500 g, 2.17 mmol), diphenylphosphinic chloride (0.617 g, 2.61 mmol), and

Et₃N (1.5 mL, 10.9 mmol) in MeCN (7.5 mL) stirred for 2.5 h, followed by purification by chromatography on SiO₂ (35% EtOAc/hexanes) provided *N*-(1-(4-chlorophenyl)cyclopropyl)ethylidene)-*P,P*-diphenylphosphinic amide (0.283 g, 33% yield) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (m, 4H), 7.38 (m, 6H), 7.29 (m, 2H), 7.23 (m, 2H), 2.30 (d, *J* = 1.9 Hz, 3H), 1.71 (dd, *J* = 7.0, 4.1 Hz, 2H), 1.26 (dd, *J* = 6.8, 3.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 192.6 (d, *J* = 7.8 Hz), 139.9, 135.3, 134.0, 133.0, 132.0, 131.3, 131.2, 131.1, 131.1, 128.4, 128.2, 128.1, 37.2 (d, *J* = 24.3 Hz), 24.8 (d, *J* = 12.3 Hz), 18.9;



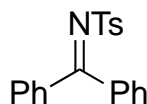
***N*-(Adamantan-1-yl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide (6f)**

According to the general procedure, using adamantyl(phenyl)methaniminium chloride **2i** (0.500 g, 1.82 mmol), diphenylphosphinic chloride (0.517 g, 2.18 mmol), and Et₃N (1.3 mL, 9.10 mmol) in MeCN (7.5 mL) stirred for 1.5 h, followed by purification by chromatography on SiO₂ (35% EtOAc/hexanes) provided *N*-(adamantan-1-yl)(phenyl)methylene)-*P,P*-diphenylphosphinic amide (0.471 g, 59% yield) as a light orange oil. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (m, 4H), 7.41 (m, 6H), 7.32 (m, 1H), 7.25 (m, 2H), 6.90 (m, 2H), 2.10 (m, 3H), 1.96 (d, *J* = 2.5 Hz, 6H), 1.74 (dd, *J* = 27.8, 12.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 196.5 (d, *J* = 12.1 Hz), 138.5 (d, *J* = 12.7 Hz), 135.1 (d, *J* = 129.0 Hz), 131.4 (d, *J* = 9.1 Hz), 130.9 (d, *J* = 2.7 Hz), 128.1, 128.0, 127.9, 127.1, 125.8, 39.6, 36.3, 28.1;



***P,P*-Diphenyl-*N*-(1-phenylpentylidene)phosphinic amide (6g)**

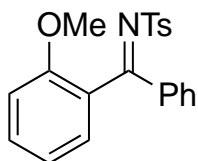
According to the general procedure, using 1-phenylpentan-1-iminium chloride **2k** (0.500 g, 2.53 mmol), diphenylphosphinic chloride (0.713 g, 3.04 mmol), and Et₃N (1.8 mL, 12.65 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on SiO₂ (35% EtOAc/hexanes) provided *P,P*-diphenyl-*N*-(1-phenylpentylidene)phosphinic amide (0.662 g, 70% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (m, 6H), 7.46 (m, 9H), 3.42 (m, 2H), 1.56 (m, 2H), 1.40 (sex, *J* = 8.5 Hz, 2H), 0.86 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 185.7 (d, *J* = 8.4 Hz), 136.4 (d, *J* = 22.5 Hz), 135.7, 134.4, 132.1, 131.5 (d, *J* = 9.1 Hz), 131.2 (d, *J* = 2.4 Hz), 128.5, 128.4, 128.2 (d, *J* = 7.3 Hz), 35.7 (d, *J* = 11.7 Hz), 30.9, 22.8, 13.7;



***N*-((Diphenyl)methylene)-4-methylbenzenesulfonamide (7a)**

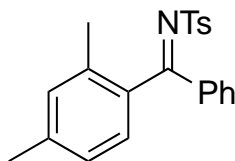
According to the general procedure, using iminium salt **2g** (0.500 g, 2.30 mmol), *p*-toluenesulfonic anhydride (0.901 g, 2.76 mmol), and Et₃N (1.59 mL, 11.5 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on SiO₂ (30% MTBE/hexanes) provided **7a** (0.741 g, 96% yield) as a white solid. ¹H NMR (CDCl₃, 400

MHz): δ 7.84 (d, J = 8.2 Hz, 2H), 7.62-7.35 (m, 10H), 7.29 (d, J = 8.1 Hz, 2H), 2.43 (s, 3H).³⁶



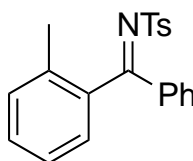
***N*-((2-Methoxyphenyl)(phenyl)methylene)-4-methylbenzenesulfonamide (7b)**

According to the general procedure, using (diphenyl)methanimine HCl **2g** (0.500 g, 2.02 mmol), *p*-toluenesulfonic anhydride (0.791 g, 2.42 mmol), and Et₃N (1.4 mL, 10.1 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on SiO₂ (30% MTBE/hexanes) provided *N*-((2-Methoxyphenyl)(phenyl)methylene)-4-methylbenzenesulfonamide (0.441 g, 60% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (dd, J = 17.6, 8.2 Hz, 4H), 7.49 (m, 1H), 7.43 (ddd, J = 7.7, 1.4 Hz, 1H), 7.33 (m, 3H), 7.24 (dd, J = 7.7, 1.8 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 3.59 (s, 3H), 2.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.6, 155.9, 143.1, 137.8, 137.0, 133.3, 131.4, 129.8, 129.1, 129.0, 128.3, 127.5, 120.1, 110.7, 55.4, 21.5.



***N*-((2,4-Dimethylphenyl)(phenyl)methylene)-4-methylbenzenesulfonamide (7c)**

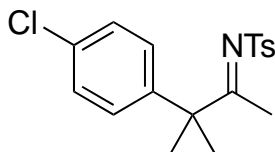
According to the general procedure, using (2,4-dimethylphenyl)(phenyl)methaniminium chloride **2a** (0.500 g, 2.02 mmol), *p*-toluenesulfonic anhydride (0.796 g, 2.44 mmol), and Et₃N (1.4 mL, 10.2 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on SiO₂ (30% MTBE/hexanes) provided *N*-((2,4-Dimethylphenyl)(phenyl)methylene)-4-methylbenzenesulfonamide (0.330 g, 45% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.83-7.80 (m, 2H), 7.70-7.68 (m, 2H), 7.53-7.49 (m, 1H), 7.37-7.33 (m, 2H), 7.28-7.26 (m, 3H), 7.08-7.06 (m, 2H), 2.41 (s, 3H), 2.10 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 178.9, 143.6, 138.0, 135.9, 135.2, 134.7, 133.9, 129.63, 129.60, 129.4, 129.3, 128.9, 127.6, 127.2, 127.1, 21.6, 19.9



***N*-((2-Methylphenyl)(phenyl)methylene)-4-methylbenzenesulfonamide (7d)**

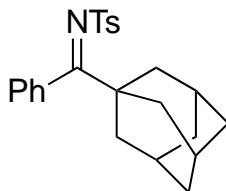
According to the general procedure, using phenyl(*o*-tolyl)methaniminium chloride **2b** (0.500 g, 2.16 mmol), *p*-toluenesulfonic anhydride (0.845 g, 2.59 mmol), and Et₃N (1.5 mL, 10.8 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on SiO₂ (30% MTBE/hexanes) provided *N*-((2-methylphenyl)(phenyl)methylene)-4-methylbenzenesulfonamide (0.694 g, 92% yield) as

a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.78-7.76 (m, 2H), 7.67-7.65 (m, 2H), 7.53-7.49 (m, 1H), 7.39-7.33 (m, 3H), 7.29-7.20 (m, 5H), 2.41 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.1, 143.5, 138.1, 136.7, 135.2, 134.9, 133.7, 130.0, 129.7, 129.4, 128.7, 127.52, 127.46, 125.3, 21.6, 19.9.



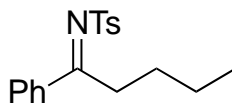
***N*-(1-(4-Chlorophenyl)cyclopropyl)ethylidene)-4-methylbenzenesulfonamide (7e)**

According to the general procedure, using (1-(4-Chlorophenyl)cyclopropyl)ethaniminium chloride **2n** (0.500 g, 2.17 mmol), *p*-toluenesulfonic anhydride (0.851 g, 2.61 mmol), and Et_3N (1.5 mL, 10.9 mmol) in MeCN (7.5 mL) stirred for 2 h, followed by purification by chromatography on SiO_2 (10% MTBE/hexanes) provided *N*-(1-(4-chlorophenyl)-cyclopropyl)ethylidene)-4-methylbenzenesulfonamide (0.720 g, 48% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 8.3 Hz, 2H), 7.30 (m, 4H), 7.24 (m, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 1.64 (dd, J = 6.9, 3.9 Hz, 2H), 1.27 (dd, J = 6.9, 3.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.5, 143.3, 138.7, 133.6, 132.0, 130.4, 129.3, 128.9, 126.8, 36.0, 23.6, 21.5, 20.2, 18.7.



***N*-(Adamantan-1-yl)(phenyl)methylene-4-methylbenzenesulfonamide (7f)**

According to the general procedure, using adamantyl(phenyl)methaniminium chloride **2i** (0.500 g, 1.82 mmol), *p*-toluenesulfonic anhydride (0.713 g, 2.18 mmol), and Et₃N (1.3 mL, 9.10 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on SiO₂ (30% MTBE/hexanes) provided *N*-(adamantan-1-yl)(phenyl)methylene-4-methylbenzenesulfonamide (0.410 g, 57% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (m, 2H), 7.36 (m, 2H), 7.28 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.06 (dd, *J* = 7.7, 1.3 Hz, 2H), 3.22 (q, *J* = 7.3 Hz, 1H), 2.40 (m, 3H), 2.01 (m, 2H), 1.79 (d, *J* = 2.6 Hz, 3H), 1.64 (dd, *J* = 37.1, 12.3 Hz, 4H), 1.12 (t, *J* = 7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 192.6, 143.0, 138.4, 134.8, 129.5, 129.2, 128.6, 127.2, 127.1, 126.9, 2126.2, 44.6, 41.9, 39.1, 27.9, 21.4, 21.4, 14.1;



***N*-(1-Phenylpentylidene)-4-methylbenzenesulfonamide (7g)**

According to the general procedure, using 1-phenylpentan-1-iminium chloride **2k** (0.500 g, 2.53 mmol), *p*-toluenesulfonic anhydride (0.991 g, 3.03 mmol), and Et₃N (1.75 mL, 12.7 mmol) in MeCN (7.5 mL) stirred for 4 h, followed by purification by chromatography on

SiO₂ (30% MTBE/hexanes) provided *N*-(1-phenylpentylidene)-4-methylbenzenesulfonamide (0.231 g, 29% yield) as a white solid.

2.4 REFERENCES

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